Icosapent Ethyl
(VASCEPA®)

Presentation to the Endocrinologic and Metabolic Drugs Advisory Committee

NDA 202057

Amarin Pharmaceuticals Ireland Limited

Agenda

REDUCE-IT History and Program Introduction	**Rebecca Juliano, PhD** *SVP, Clinical Research and Development* *Amarin*
Medical Need	**Michael Miller, MD** *Professor of Cardiovascular Medicine* *Director, Center for Preventive Cardiology* *University of Maryland School of Medicine*
REDUCE-IT Trial Summary • ***Study Overview*** • ***Study Results***	**Deepak L. Bhatt, MD, MPH** *Executive Director of Interventional Cardiovascular Programs, Brigham and Women's Hospital* *Professor, Harvard Medical School*
Clinical Implications of REDUCE-IT	**Ann Marie Navar, MD, PhD** *Assistant Professor of Cardiology* *Duke University School of Medicine* *Duke Clinical Research Institute*
Closing Remarks	**Rebecca Juliano, PhD** *SVP, Clinical Research and Development* *Amarin*

Additional External Consultants

- Christie M. Ballantyne, MD – Baylor College of Medicine
- Linet Bolar, MD – Fiore Healthcare Advisors, Inc.
- Robert S. Busch, MD – Albany Medical Center
- John Chapman, PhD, DSc – Pitié-Salpêtrière University Hospital
- Charles Michael Gibson, MD – Beth Israel Deaconess Medical Center
- Robert Patrick Giugliano, MD, MSc - Brigham and Women's Hospital
- Judith D. Goldberg, ScD – NYU Langone
- Peter R. Kowey, MD – The Lankenau Institute for Medical Research
- Paul Ridker, MD, MPH – Brigham and Women's Hospital
- Paul D. Rosenblit, MD, PhD – UC Irvine School of Medicine

REDUCE-IT History and Program Introduction

Rebecca Juliano, PhD

SVP, Clinical Research and Development

Amarin

Amarin Corporation

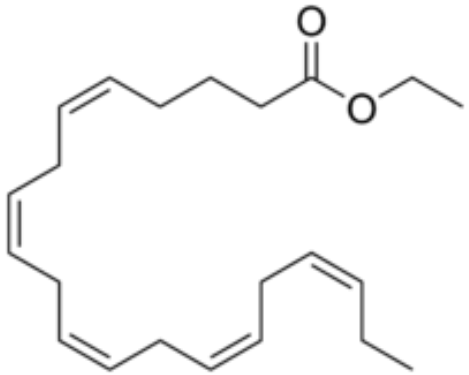
- Committed to leadership in lipid sciences for over two decades, prioritizing potential cardiac benefits of omega-3 fatty acids
- Supported >100 scientific publications and presentations
- Focused on the development of Vascepa® (icosapent ethyl) for over a decade

Icosapent Ethyl

Unique Molecule with Substantial History of Clinical Use

- Highly purified, concentrated and stable ethyl ester of eicosapentaenoic acid (EPA) [20:5, n-3]
  - All-cis-ethyl 5,8,11,14,17-icosapentaenoate

- FDA approved since July 2012 for the treatment of very high TG (≥500 mg/dL)
  - >37,000 patient years in clinical studies
  - >8 million prescriptions
  - Low post-marketing adverse event rates



TG Indication Supported by MARINE & ANCHOR

	MARINE (N=229) NCT01047683	ANCHOR (N=702) NCT01047501	REDUCE-IT (N=8179) NCT01492361
Key Inclusion	Severe HTG	Statin Controlled LDL-C with Elevated TGs	Statin controlled LDL-C with elevated TGs
CV Risk	--	High risk for CVD	High risk for CVD
TG Level	≥500 to ≤2000 mg/dL	≥200 to <500 mg/dL	≥135 to <500 mg/dL
Primary Endpoint	TG Reduction	TG Reduction	CV Events
Timing (years)	2009-2011	2009-2011	2011-2018

Abbreviations: CV=cardiovascular; CVD=cardiovascular disease; HTG=hypertriglyceridemia; LDL-C=low density lipoprotein cholesterol; TG=triglycerides

All studies conducted as Phase 3 studies under SPA agreements with FDA

The Need for an Icosapent Ethyl CVOT

- TG is likely a marker of CV risk, but TG has not been proven to be a modifiable risk factor
- CVOTs testing low-dose mixed omega-3 fatty acids in statin-treated patients have not demonstrated benefit
- High-dose stable EPA appeared different
  - EPA is unique from other omega-3 fatty acids
  - TG-lowering and other putative mechanisms of reducing CV risk
  - JELIS is supportive but not conclusive

REDUCE-IT Designed to Address CV Outcomes After Successful Biomarker-Focused Studies

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REDUCE-IT Design

- Trial design and two protocol amendments were agreed with FDA under a Special Protocol Assessment agreement; key amendment updates made while blinded and included:
  - Amendment 1 increased qualifying TG lower limit to 200 mg/dL for remaining enrollment to ensure broader TG spectrum represented
  - Amendment 2 elevated hard MACE as the key secondary endpoint per Steering Committee and FDA input
- Prospective, randomized, double-blind, placebo-controlled, multinational study
  - 8179 patients from 11 countries studied for a median of 4.9 years
  - Patients broadly managed for risk with modern modalities
  - CV outcomes focus of the study, not biomarkers
  - Designed to test a single primary endpoint of composite MACE
- Designed to test the CV benefit of icosapent ethyl
  - By design cannot answer separate questions of potential CV benefit from TG-lowering or other omega-3 products

Bhatt DL, Steg PG, Miller M, et al. N Engl J Med. 2018;380(1):11-22. doi:10.1056/NEJMoa1812792

REDUCE-IT Results

- Substantial CV risk reduction that is statistically significant and generally consistent across endpoints and subgroups
- Well-tolerated with safety findings that can be addressed within labeling

Bhatt DL, Steg PG, Miller M, et al. N Engl J Med. 2018;380(1):11-22. doi:10.1056/NEJMoa1812792

Seeking Indication for CV Risk Reduction Consistent with REDUCE-IT

- Amarin looks forward to labeling discussions with FDA leading to final indication wording and label content that communicate REDUCE-IT efficacy and safety results
- REDUCE-IT enrolled high-risk patients including the following key defining characteristics:
  - LDL-C controlled on stable statin therapy
  - Persistently elevated TG levels as a marker of risk
  - Patients with established CVD or high-risk primary prevention patients with diabetes and other CV risk factors

Amarin Aims to Address FDA Discussion Topics

- Robustness of efficacy results, including:
  - First-in-class CV outcomes indication based on REDUCE-IT results
  - Mineral oil placebo considerations
  - Magnitude and clinical relevance of the treatment effect
  - Robustness of the individual components of the primary and key secondary composite endpoints
- Label representation of safety finding (atrial fibrillation/flutter and bleeding)
- Evidence of CV benefit within CV Risk Cohort 2 (diabetes); considering:
  - Age
  - Diabetes
  - Additional CVD risk factors
  - LDL-C levels
  - TG levels
  - Statin intensity
  - Other factors
- Sufficiency of efficacy and safety evidence for CV risk reduction indication

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Closing Remarks	**Rebecca Juliano, PhD** *SVP, Clinical Research and Development* *Amarin*

The Need:
Addressing High Cardiovascular Risk in Adults with Persistently Elevated Triglyceride Levels

Michael Miller, MD

Professor of Cardiovascular Medicine, Epidemiology & Public Health

Director, Center for Preventive Cardiology

University of Maryland School of Medicine

Disclosure

Dr. Miller is a Steering Committee Member for the REDUCE-IT Trial and scientific advisor to Amarin

High CV Risk Patients
The Unmet Need

- CV disease is a large and growing unmet need
  - 605,000 new and 200,000 recurrent heart attacks per year in the US (**~ 1 every 40 seconds**)
  - Stroke rates are similar, accounting for 1 of every 19 US deaths (**~ 1 every 40 seconds**)
  - >800,000 CV deaths each year (**~ 1 every 38 seconds**)
- Current therapies for managing cholesterol, diabetes, hypertension, and other risks are not enough; significant residual risk remains

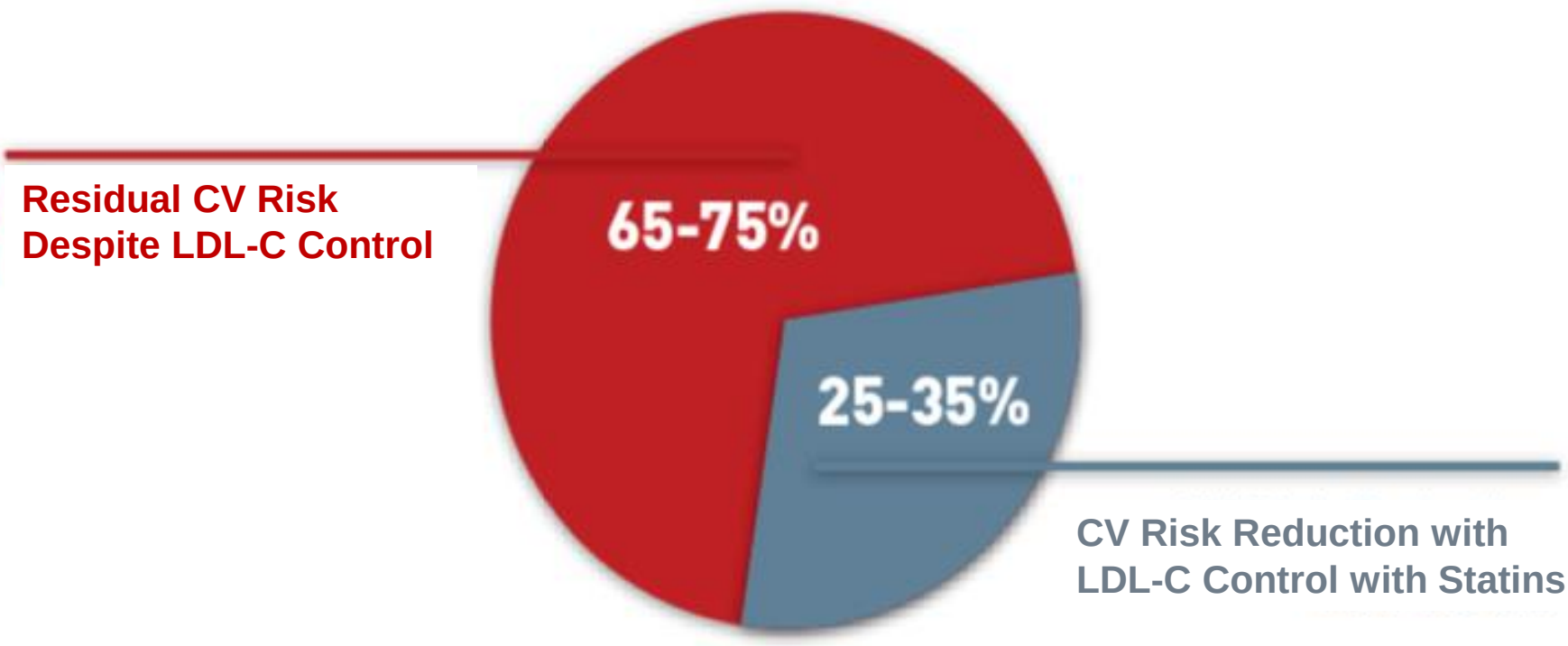
AHA: Heart Disease and Stroke Statistics 2019 At-a-Glance

Residual CV Risk Exists for Statin-Treated Patients

Despite Being Well-managed on Modern Therapies

~65-75% residual CV risk beyond current standard of care[1]

- Residual CV risk remains high even with controlled LDL-C
- Increased LDL-C control does not eliminate CV risk



1) Ganda OP, Bhatt DL, Mason RP, Miller M, Boden WE. Unmet need for adjunctive dyslipidemia therapy in hypertriglyceridemia management. J Am Coll Cardiol. 2018.

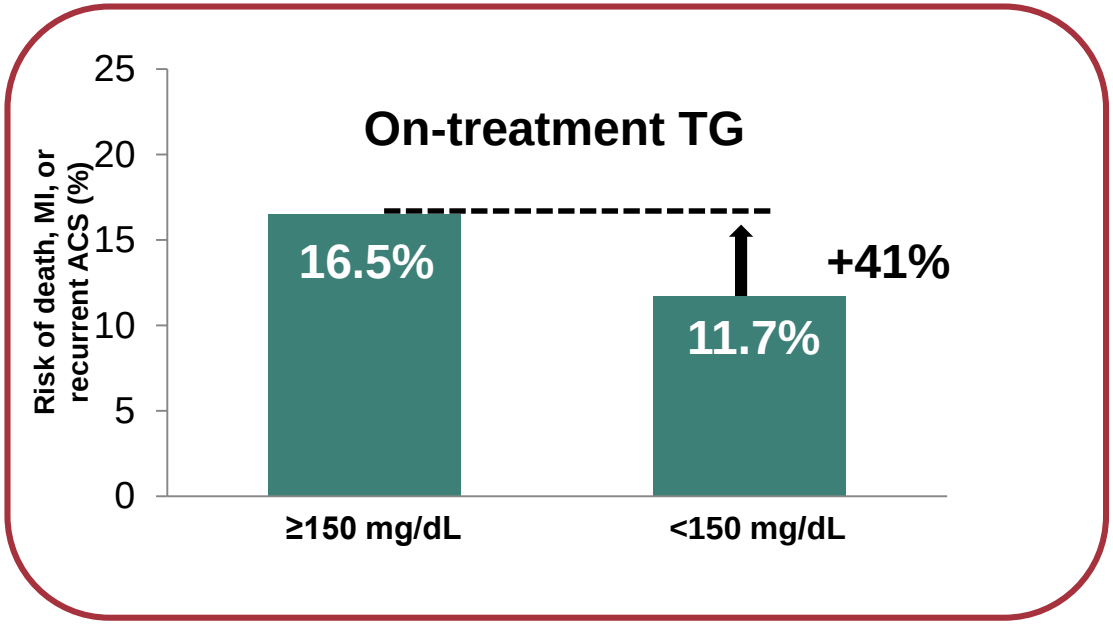
The Unmet Need Despite Statin-controlled LDL-C
Identifying High CV Risk Patients

- High CV event rates in patients with residual CV risk
  - Limited options for patients with residual CV risk
  - Urgent need for new treatment options
- Common risk factors beyond LDL-C control
  - Persistently elevated TG levels
  - Prior MACE event
  - Diabetes
- REDUCE-IT inclusion criteria correlate with other disease parameters in high-risk patients
  - Convergence of multiple risk factors with persistently elevated TG; a CV risk enhancer

PROVE-IT

Residual Elevated TG Predicts CVD Risk Despite Statin

Despite achieving LDL-C <70 mg/dL with a high-dose statin, patients with ***TG ≥150 mg/dL have a 41% higher risk*** of coronary events*



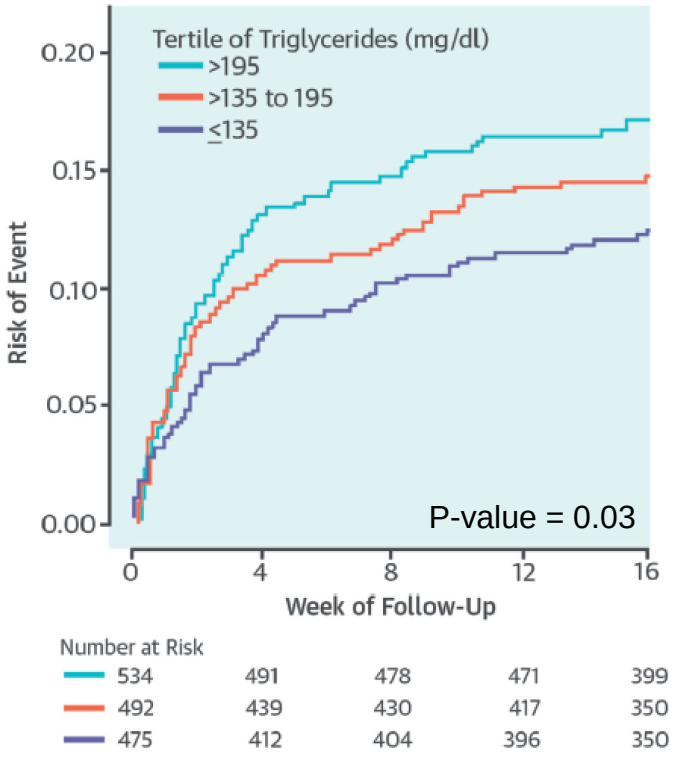
Miller M, Cannon CP, Murphy SA, et al. *J Am Coll Cardiol*. 2008;51:724-30.
***Death, myocardial infarction, or recurrent acute coronary syndrome, PROVE-IT-TIMI 22**

Residual Elevated TG as a Clinical Marker of Risk

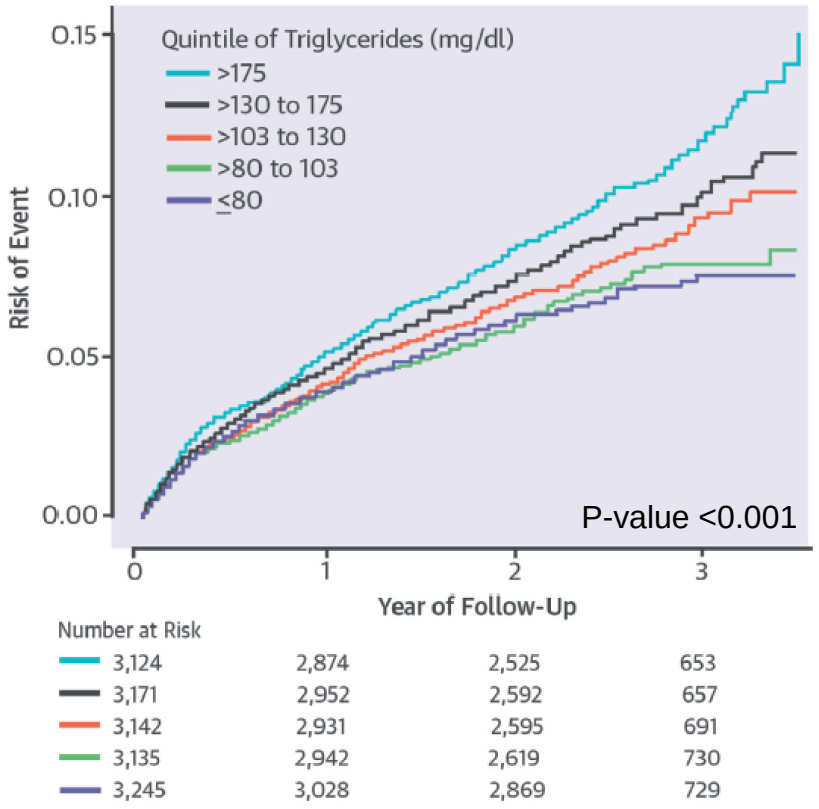
Elevated TG Despite Statin Associated with CHD Risk

- MIRACL >3000 statin-treated patients with recent Acute Coronary Syndrome (ACS)
- Dal-OUTCOMES >15,000 statin-treated patients with recent ACS

MIRACL: Short-Term Risk after ACS



Dal-OUTCOMES: Long-Term Risk after ACS



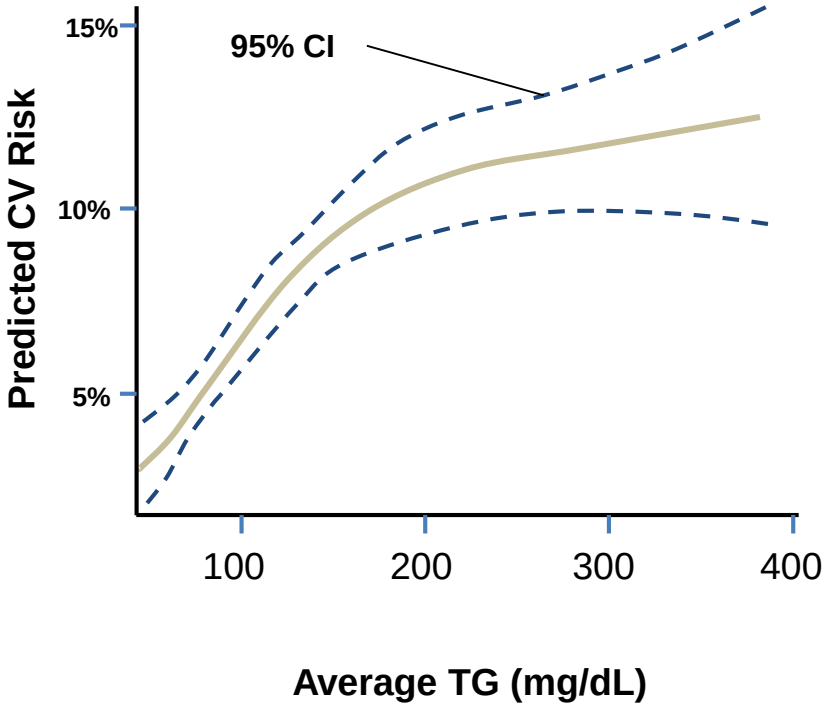
Increasing risk for each TG cut above 100 mg/dL

Schwartz GG et al. JACC 2015:65(21):2267-75.

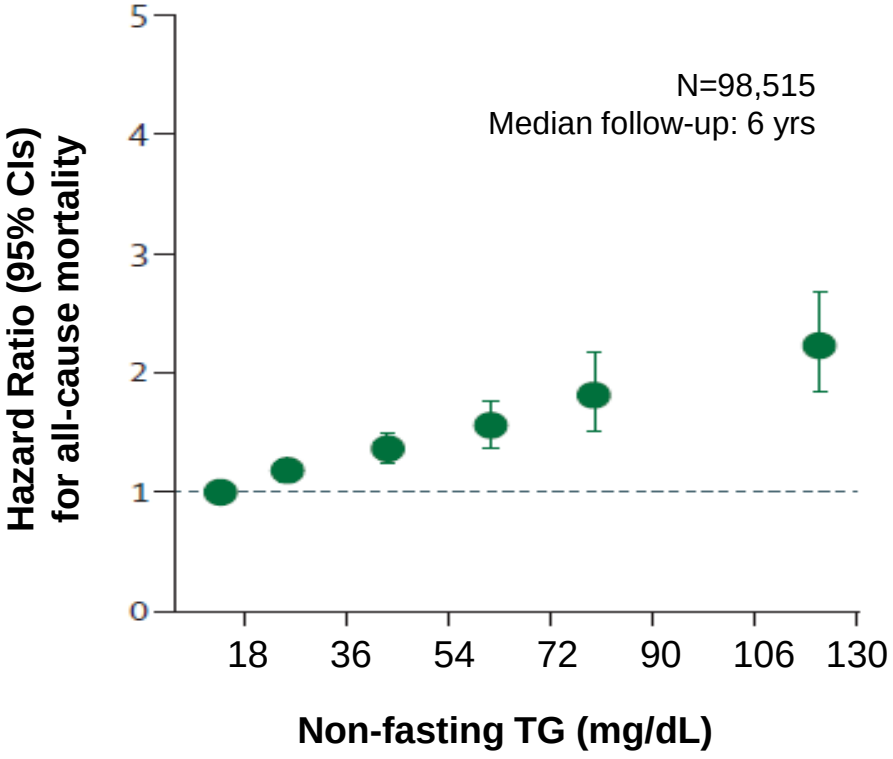
Lifetime Elevated TG as a Clinical Marker of Risk

Risk at <100 mg/dL and Plateaus Begins Around 200 mg/dL

10-Year CV Risk[1]



Copenhagen Heart Study[2]
All-Cause Mortality



1. Navar AM et al. March 18, 2019; New Orleans, LA.
2. Nordestgaard BG, Varbo A. Lancet. 2014;384:626-635. doi:10.1016/S0140-6736(14)61177-6

TG: Marker of CV Risk vs. Modifiable Risk Factor

- Elevated TG correlates with elevated CV risk
  - Supported by epidemiological, genetic, and clinical data
  - TG-rich lipoproteins (TRL) promote
    - Increased concentration of LDL particles[1]
    - Activation of platelets & thrombosis[2]
    - Remnant deposition and inflammation[3]
- TG as a modifiable risk factor remains to be established
  - CVOT subgroup analyses suggest benefit in patients with dyslipidemia, but not in the full patient cohorts (e.g. ACCORD-Lipid, AIM-HIGH)
  - Therapies that lower TG along with other putative mechanisms of benefit cannot alone prove or negate TG-lowering as beneficial for CV risk reduction

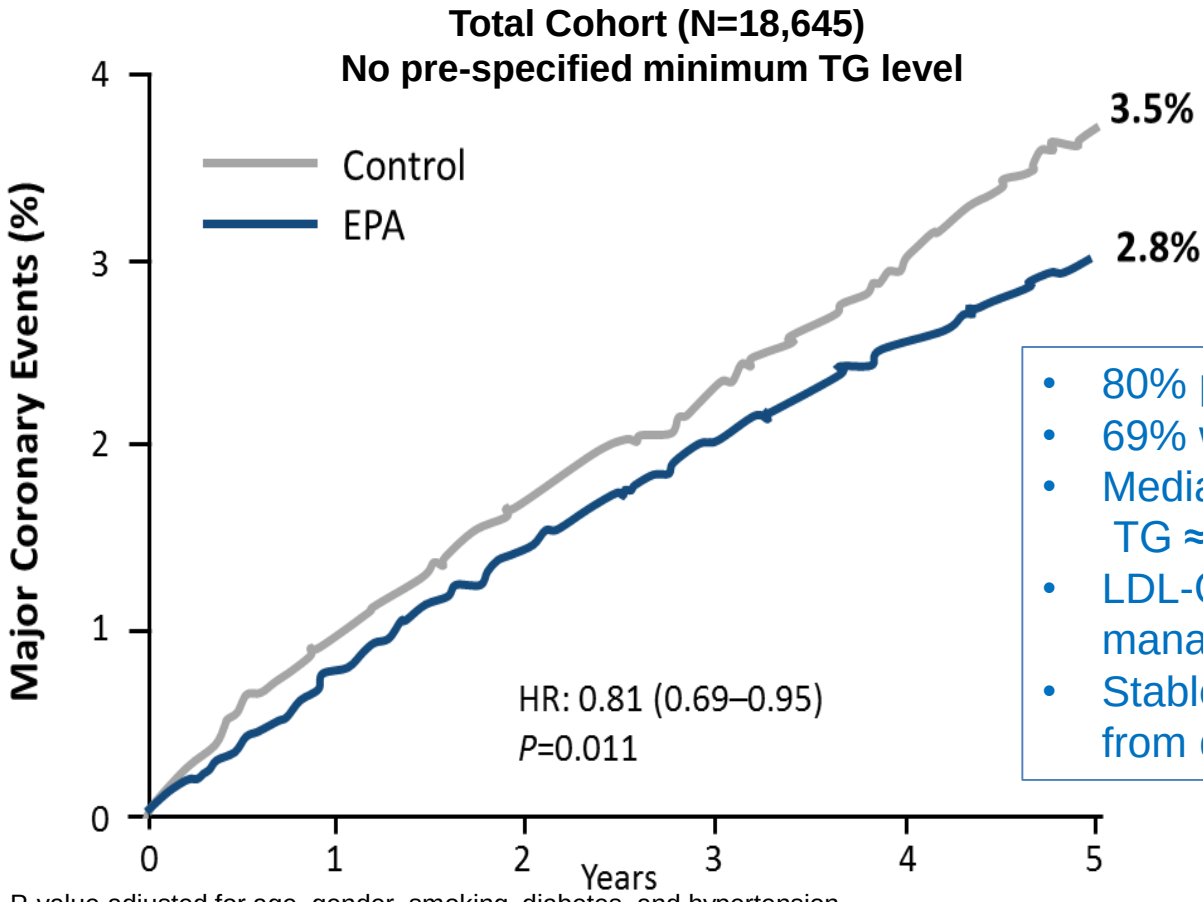
1) Miller M. J Am Coll Cardiol. 2018;72:170-2; Saeed A et al. J Am Coll Cardiol. 2018;72:156-69.
2) After Reiner Ž. Nat Rev Cardiol. 2017;14:401-11.
3) Nordestgaard BG.Circ Res. 2016;118:547-563; Nordestgaard BG, Varbo A. Lancet. 2014;384:626-635.

Apparent Mixed Signals from Omega-3 CVOTs
Differences in Omega-3 Type and Dose

- Early low-dose, mixed omega-3 CVOTs without concomitant statin use suggested benefit (e.g., GISSI-P)
- Recent low-dose, mixed omega-3 CVOTs do not suggest benefit when added to statin and other modern therapies (e.g., OMEGA, Alpha-Omega, ORIGIN, VITAL, ASCEND)
- JELIS was distinct in reporting CV benefit
  - Caveats to study design; supportive, not conclusive
  - Unique omega-3: Stable EPA-only (not all omega-3s are the same)
  - Unique dose: High plasma EPA levels achieved
  - CV benefit not fully explained by ~5% reduction in TGs

JELIS: First CVOT Reporting Benefit of EPA

Japanese patients with elevated TC randomized to statin alone or statin + Ethyl-EPA (1.8 g/day Epadel) in PROBE Study Design (open label; blinded endpoint adjudication)



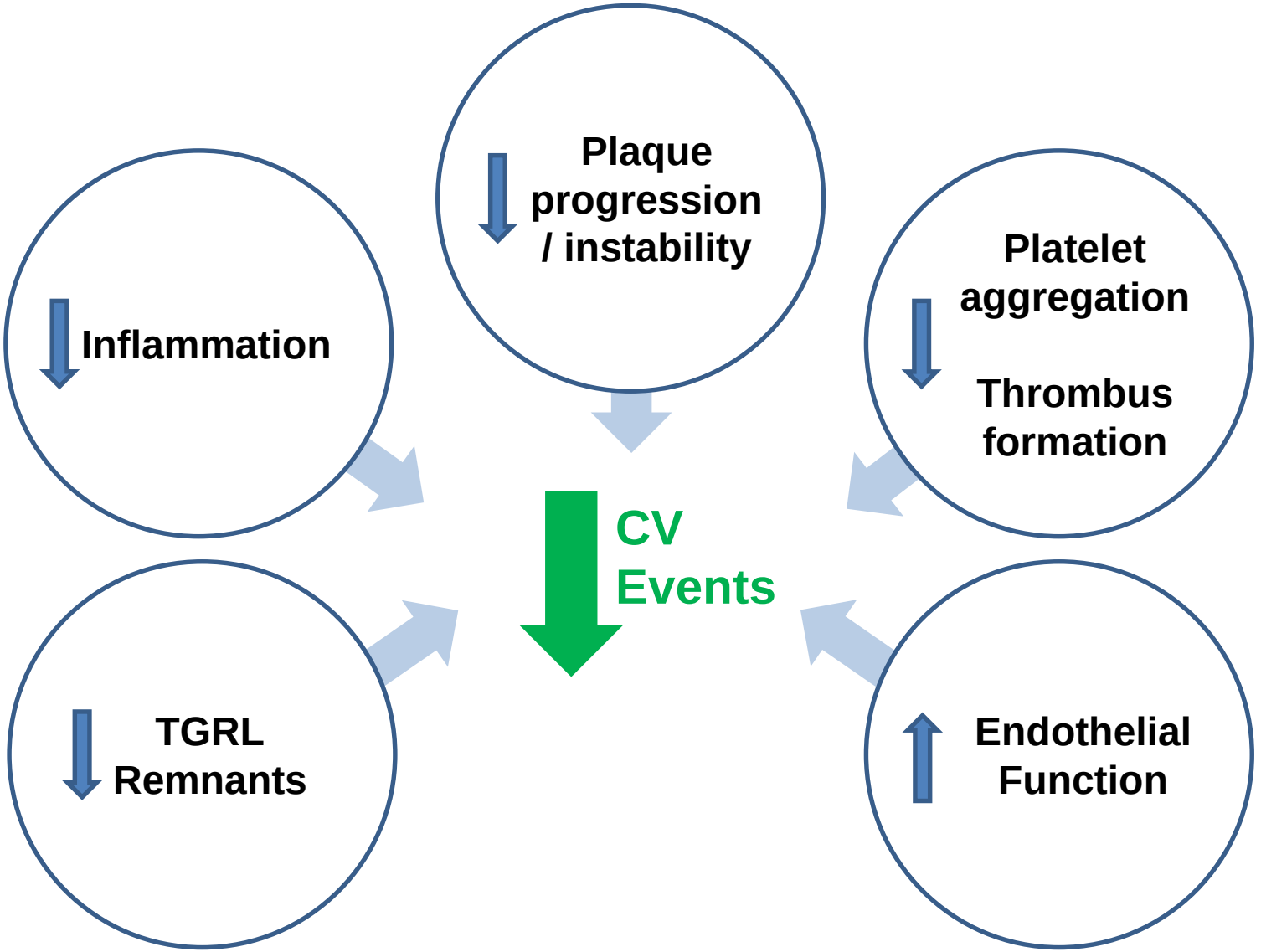
–19% RRR
(5% TG reduction)

- 80% primary prevention
- 69% women
- Median statin-naïve baseline TG ≈154 mg/dL (IQR 110-221)
- LDL-C ≈135 mg/dL with statin; managed per Japanese guidelines
- Stable form of EPA (protected from degradation)

P-value adjusted for age, gender, smoking, diabetes, and hypertension
PROBE = Prospective Randomized Open-label Blinded Endpoint evaluation

JELIS: Yokoyama Lancet 2007;369:1090–98

Potential CV-related Mechanisms of Action of EPA



Post-JELIS Questions For EPA Therapy

- Would similar benefit be observed in:
  - A blinded, placebo-controlled study?
  - A broader patient population including US patients?
    - Higher prevalence of other risk factors including diabetes and hypertension
  - Patients with higher CV risk, including:
    - More secondary prevention patients?
    - Patients with elevated TG despite statin therapy?
  - Patients with residual risk despite more aggressive statin therapy and LDL-C control?
- There remains an unmet medical need for patients with elevated TG levels and other residual risk identifiers beyond statin-controlled LDL-C
  - REDUCE-IT designed to test the benefit of icosapent ethyl in such patients

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REDUCE-IT Trial Summary

Deepak L. Bhatt, MD, MPH

Executive Director of Interventional Cardiovascular Programs, Brigham and Women's Hospital

Professor, Harvard Medical School

Disclosure

Dr. Bhatt discloses research funding from Amarin Pharma, Inc. to Brigham and Women's Hospital for his role as Study Chair and PI of REDUCE-IT.

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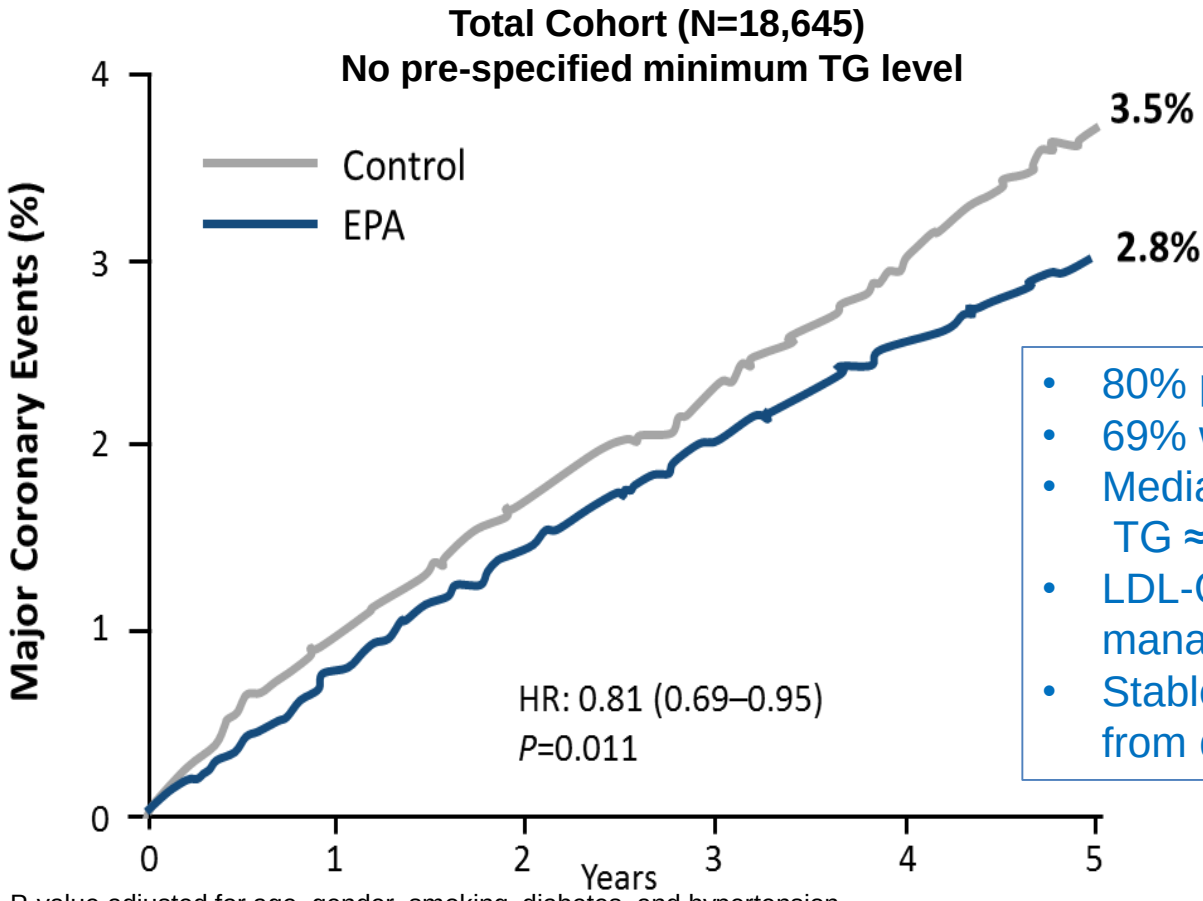

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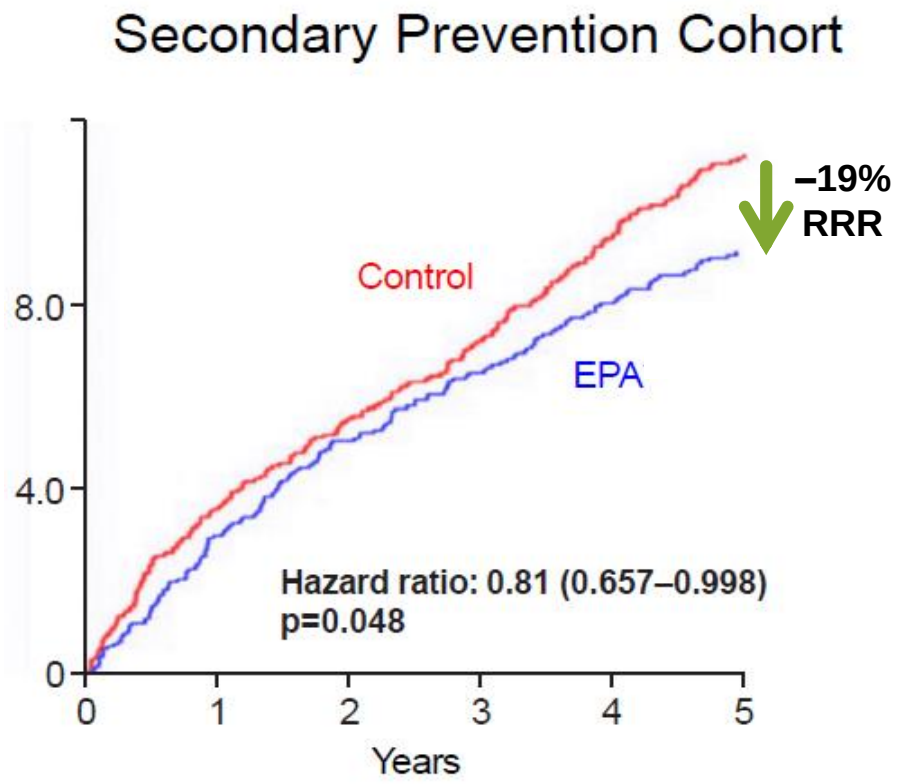
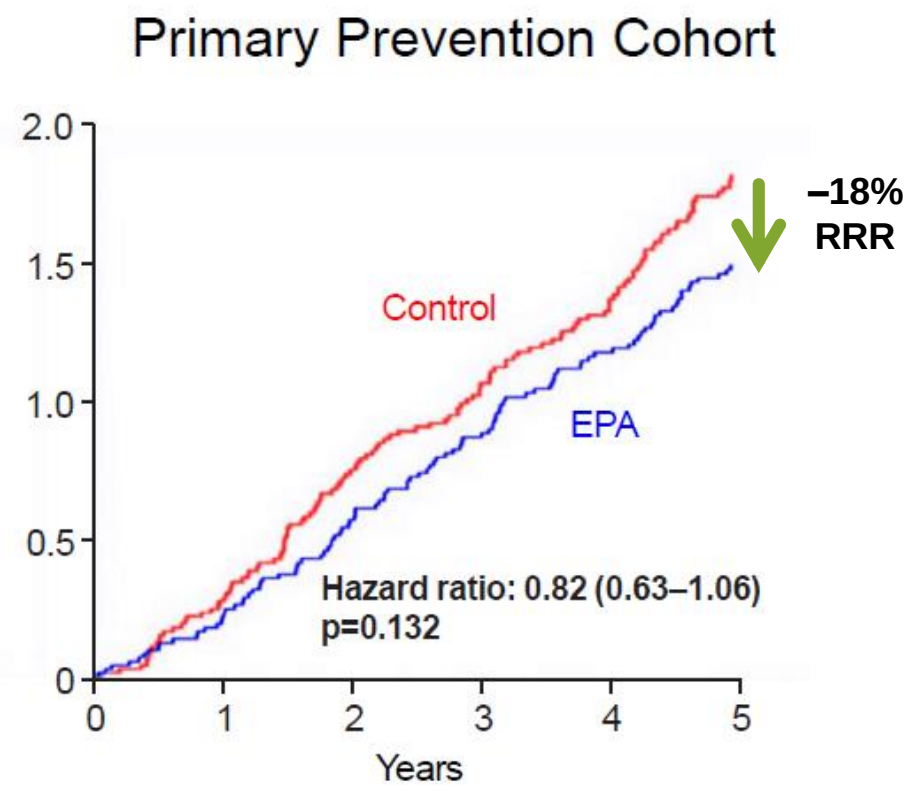
JELIS: First CVOT Reporting Benefit From EPA

Japanese patients with elevated TC randomized to statin alone or statin + Ethyl-EPA (1.8 g/day Epadel) in PROBE Study Design (open label; blinded endpoint adjudication)

Total Cohort (N=18,645)
No pre-specified minimum TG level





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REDUCE-IT
Trial Overview

- Multinational, randomized, double-blind, placebo-controlled study
- Evaluated icosapent ethyl 4 g/day in statin-treated patients with controlled LDL-C, moderately elevated TG levels, and CV risk
- Designed with an approximate sample size of 7,990 patients and follow-up until approximately 1,612 events (90% power to detect a 15% RRR with $p < 0.05$)
- Primary endpoint was time-to-first major adverse CV event (MACE)

REDUCE-IT: Study Oversight

Global Principal Investigator

Deepak L. Bhatt MD, MPH, Professor of Medicine at Harvard Medical School, Executive Director of Interventional Cardiovascular Programs at Brigham and Women's Hospital Heart & Vascular Center

Steering Committee

Deepak L. Bhatt MD, MPH (Chair), Christie M. Ballantyne MD, Eliot A. Brinton MD, Terry A. Jacobson MD, Michael Miller MD, Ph. Gabriel Steg MD, Jean-Claude Tardif MD

Data Monitoring Committee (Monitored safety signals, performed pre-specified interim analyses)

Brian Olshansky MD (Chair), Mina Chung MD, Al Hallstrom PhD, Lesly A. Pearce MS (non-voting independent statistician)

Independent Statistical Validation

- Stuart J. Pocock PhD, John Gregson PhD; London School of Tropical Medicine and Hygiene
- Jane J. Lee PhD, Xiaohua Chen MS, Qi Gao MS; Baim Clinical Research Institute

Clinical Endpoint Committee (Medical experts blinded to treatment; identified and adjudicated outcome events)

C. Michael Gibson MD, MS (Chair), Anjan K. Chakrabarti MD, MPH, Eli V. Gelfand MD, Robert P. Giugliano MD, SM, Megan Carroll Leary MD, Duane S. Pinto MD, MPH, Yuri B. Pride MD

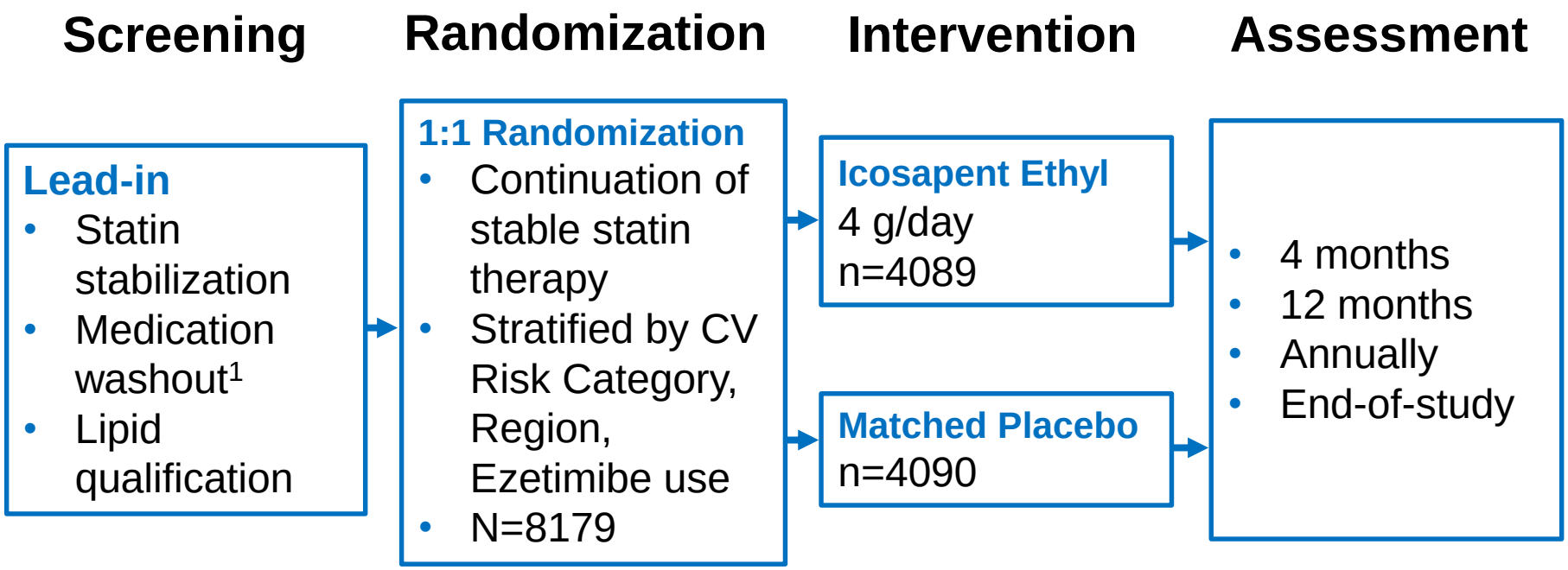
REDUCE-IT

Design: Key Inclusion/Exclusion Criteria

- Key Inclusion Criteria
  - Stabilized statin therapy ≥4 weeks prior to randomization
    - TG level of ≥135 - <500 mg/dL*
    - LDL-C level of >40 - ≤100 mg/dL
  - CV Risk Cohort 1: Secondary prevention
    - Established CVD
    - Age ≥45 years
  - CV Risk Cohort 2: High-risk primary prevention with diabetes
    - Diabetes requiring medication
    - Age ≥50 years
    - ≥1 additional risk factor for CVD
- Key Exclusion Criteria
  - Severe heart failure (Class IV)
  - Severe liver disease
  - Pancreatitis
  - Fish/shellfish allergy
  - Statin intolerance
  - HbA1c > 10.0%
  - Uncontrolled Hypertension

*Fasting TG levels ≥135 mg/dL since a 10% variance against 150 mg/dL enrollment criteria was allowed

REDUCE-IT
Design



[1]Patients remained on statins and therapies for other medical conditions (e.g., hypertension, diabetes antiplatelets), but washed-out of therapies that affect TG levels (e.g., omega-3s, fibrates, niacin). icosapent ethyl and placebo were administered as 2g twice daily with food.

Pharmaceutical grade mineral oil, selected based on color and consistency match in conjunction with FDA input

Adapted from Bhatt DL, Steg PG, Brinton EA, et al; on behalf of the REDUCE-IT Investigators. *Clin Cardiol*. 2017;40:138-148.

REDUCE-IT

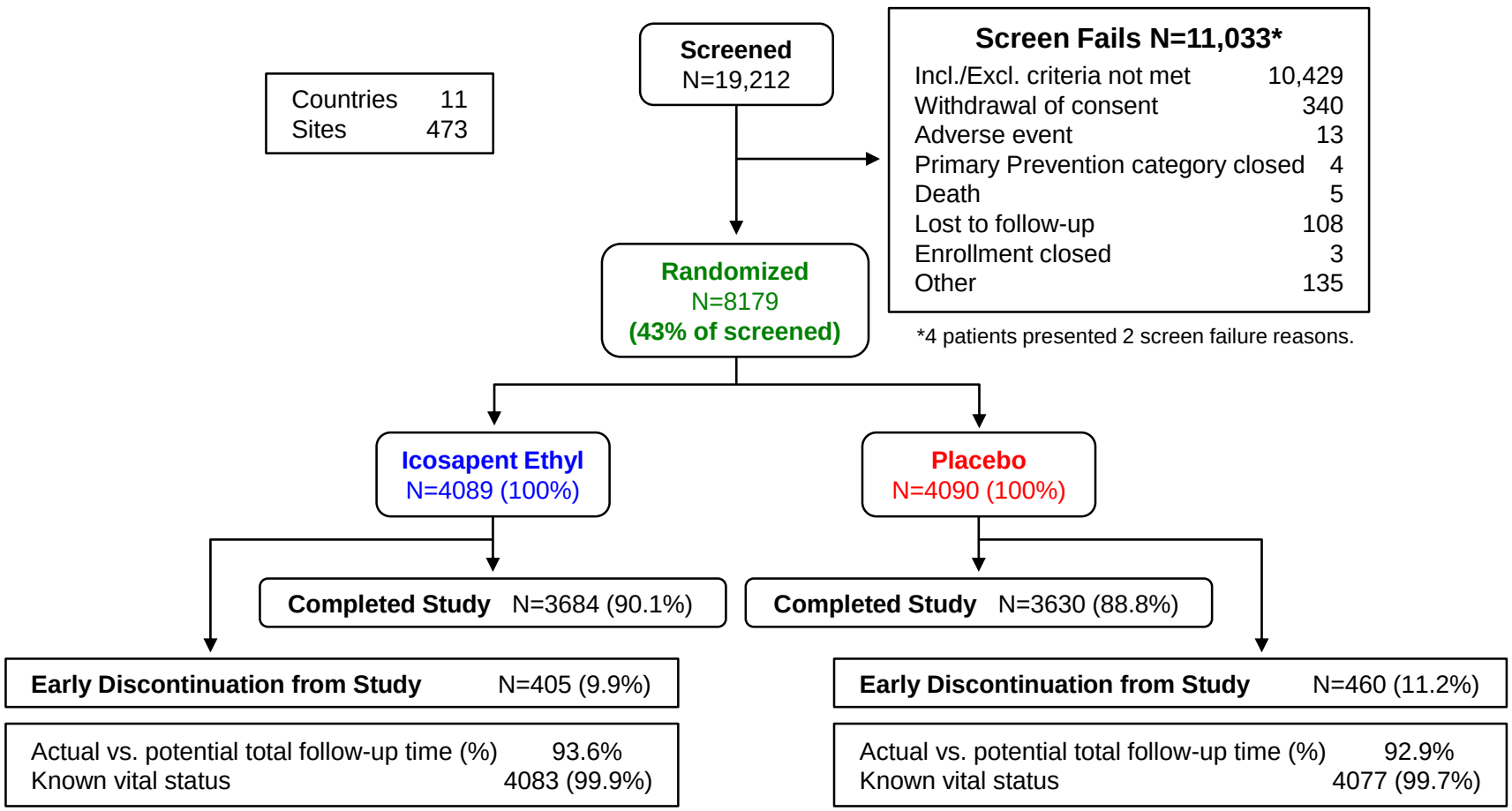
Design: Trial Endpoints

- **Primary Endpoint:** Time-to-first occurrence of composite Major Adverse Cardiac Events (MACE)
  - CV death
  - Nonfatal myocardial infarction (MI)
  - Nonfatal stroke
  - Coronary revascularization
  - Unstable angina requiring hospitalization
- **Key Secondary Endpoint:** Time-to-first occurrence of composite of CV death, nonfatal MI, or nonfatal stroke
- Secondary CV endpoints with predefined hierarchical statistical testing
- Tertiary and exploratory endpoints

Bhatt DL, Steg PG, Miller M, et al. N Engl J Med. 2019; 380:11-22.

REDUCE-IT Efficacy Results

CONSORT Diagram



Median trial follow up duration was 4.9 years.

Bhatt DL, Steg PG, Miller M, et al. N Engl J Med. 2019; 380:11-22.

Design
Baseline Characteristics

	Icosapent Ethyl (N=4089)	Placebo (N=4090)
Age (years), Median (Q1-Q3)	64.0 (57.0–69.0)	64.0 (57.0–69.0)
Female, n (%)	1162 (28.4)	1195 (29.2)
Non-White, n (%)	398 (9.7)	401 (9.8)
Westernized Region, n (%)	2906 (71.1)	2905 (71.0)
CV Risk Category, n (%)		
Secondary-prevention cohort	2892 (70.7)	2893 (70.7)
Primary-prevention cohort	1197 (29.3)	1197 (29.3)
Ezetimibe Use, n (%)	262 (6.4)	262 (6.4)
Statin Intensity, n (%)		
Low	254 (6.2)	267 (6.5)
Moderate	2533 (61.9)	2575 (63.0)
High	1290 (31.5)	1226 (30.0)
Type 2 Diabetes (T2DM), n (%)	2367 (57.9)	2363 (57.8)
HbA1c in Patients with T2DM, median % (Q1,Q3)	7.0 (6.3, 7.8)	7.0 (6.3, 7.9)
Triglycerides (mg/dL), Median (Q1-Q3)	216.5 (176.5–272.0)	216.0 (175.5–274.0)
HDL-C (mg/dL), Median (Q1-Q3)	40.0 (34.5–46.0)	40.0 (35.0–46.0)
LDL-C (mg/dL), Median (Q1-Q3)	74.0 (61.5–88.0)	76.0 (63.0–89.0)
Triglycerides Category, n (%)		
<150 mg/dl	412/4086 (10.1)	429/4089 (10.5)
≥150 to <200 mg/dl	1193/4086 (29.2)	1191/4089 (29.1)
≥200 mg/dl	2481/4086 (60.7)	2469/4089 (60.4)

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med*. 2018.

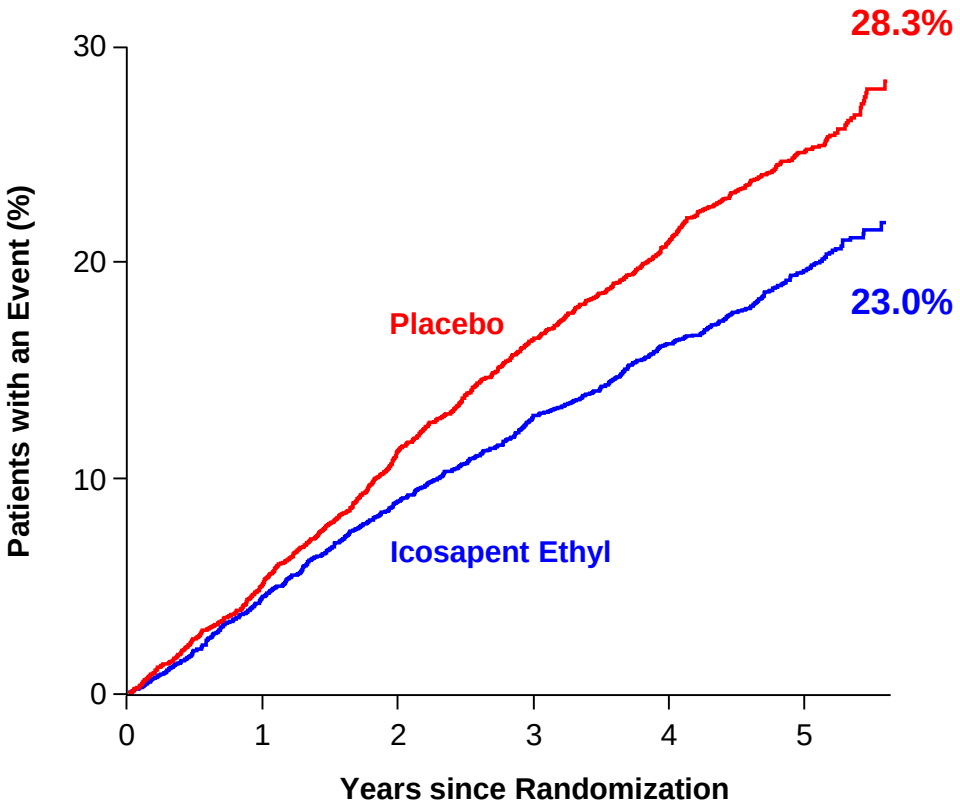
Key Baseline Medications

	Icosapent Ethyl (N=4089)	Placebo (N=4090)
Antiplatelet	3257 (79.7%)	3236 (79.1%)
One Antiplatelet	2416 (59.1%)	2408 (58.9%)
Two or More Antiplatelets	841 (20.6%)	828 (20.2%)
Anticoagulant	385 (9.4%)	390 (9.5%)
ACEi or ARB	3164 (77.4%)	3176 (77.7%)
Beta Blocker	2902 (71.0%)	2880 (70.4%)
Statin	4077 (99.7%)	4068 (99.5%)

Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019;73:2791-2802.

Primary Endpoint Achieved

Composite: CV death, nonfatal MI, nonfatal stroke, coronary revascularization, unstable angina



Hazard Ratio, 0.75
(95% CI, 0.68–0.83)

RRR = 24.8%

ARR = 4.8%

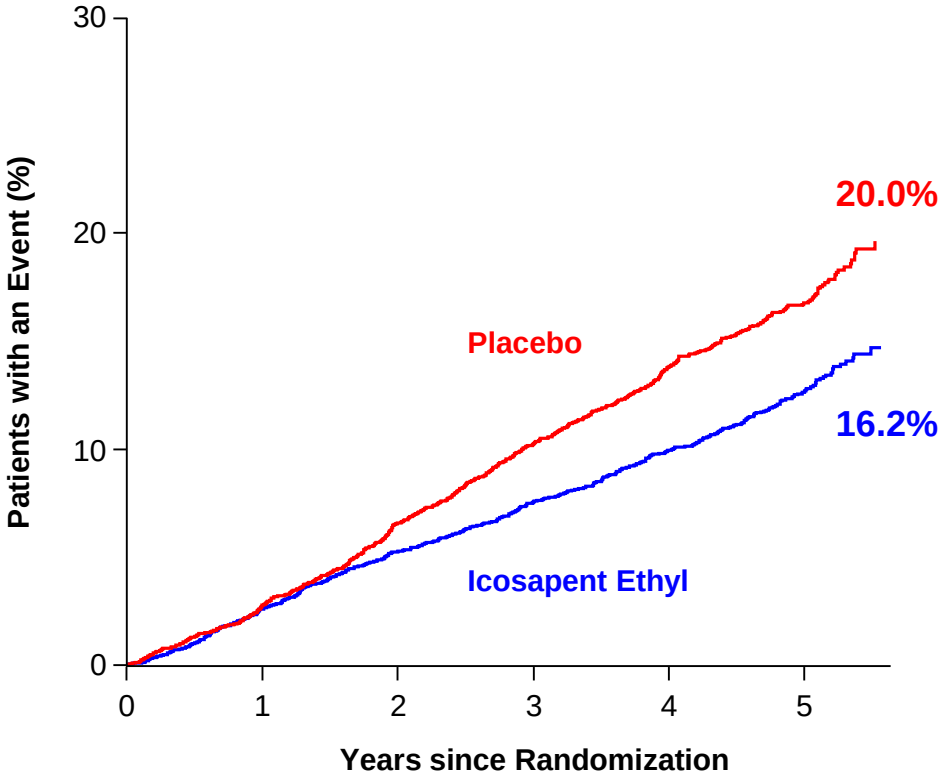
NNT = 21 (95% CI, 15–33)

P=0.00000001

Estimated Kaplan-Meier event rate at approximately 5.7 years

Key Secondary Endpoint Achieved

Composite: CV death, nonfatal MI, nonfatal stroke



Hazard Ratio, 0.74
(95% CI, 0.65–0.83)

RRR = 26.5%

ARR = 3.6%

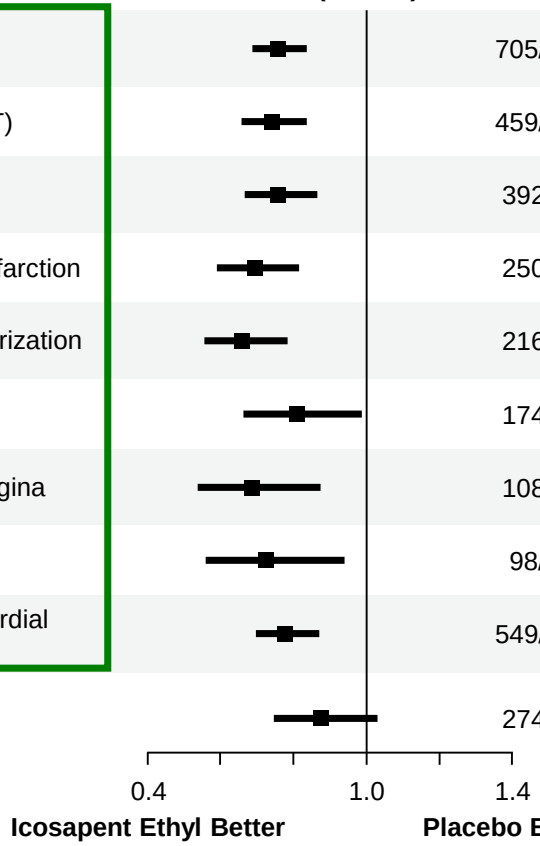
NNT = 28 (95% CI, 20–47)

P=0.0000006

Estimated Kaplan-Meier event rate at approximately 5.7 years

Prespecified Hierarchical Endpoint Testing

Endpoint	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	RRR	P-value
Primary Composite (ITT)	705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68–0.83)	25%▼	<0.001
Key Secondary Composite (ITT)	459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65–0.83)	26%▼	<0.001
Cardiovascular Death or Nonfatal Myocardial Infarction	392/4089 (9.6%)	507/4090 (12.4%)	0.75 (0.66–0.86)	25%▼	<0.001
Fatal or Nonfatal Myocardial Infarction	250/4089 (6.1%)	355/4090 (8.7%)	0.69 (0.58–0.81)	31%▼	<0.001
Urgent or Emergent Revascularization	216/4089 (5.3%)	321/4090 (7.8%)	0.65 (0.55–0.78)	35%▼	<0.001
Cardiovascular Death	174/4089 (4.3%)	213/4090 (5.2%)	0.80 (0.66–0.98)	20%▼	0.03
Hospitalization for Unstable Angina	108/4089 (2.6%)	157/4090 (3.8%)	0.68 (0.53–0.87)	32%▼	0.002
Fatal or Nonfatal Stroke	98/4089 (2.4%)	134/4090 (3.3%)	0.72 (0.55–0.93)	28%▼	0.01
Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke	549/4089 (13.4%)	690/4090 (16.9%)	0.77 (0.69–0.86)	23%▼	<0.001
Total Mortality	274/4089 (6.7%)	310/4090 (7.6%)	0.87 (0.74–1.02)	13%▼	0.09

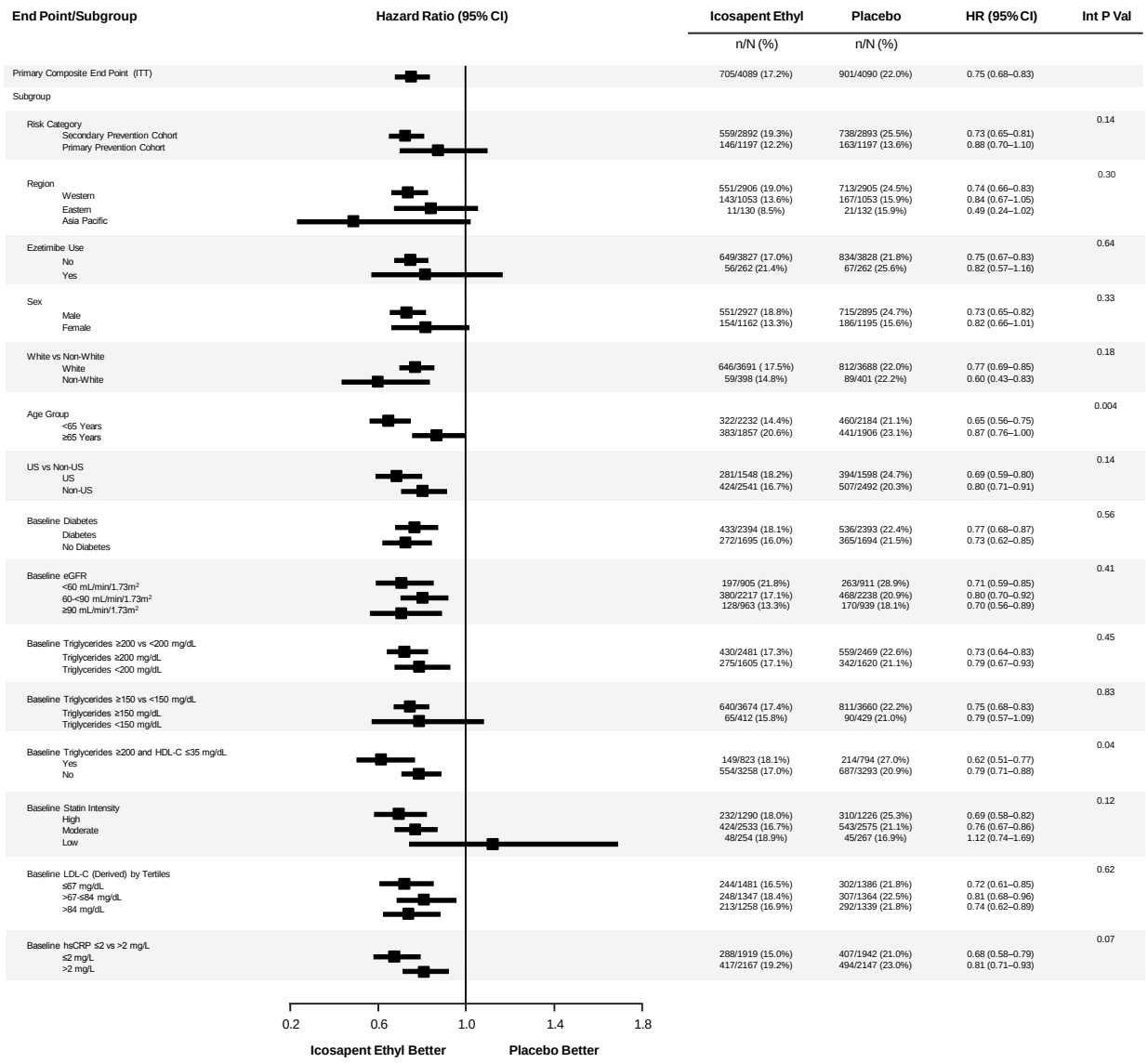


RRR denotes relative risk reduction

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019; 380:11-22. Bhatt DL. AHA 2018, Chicago.

Primary Endpoint Consistent in Subgroups

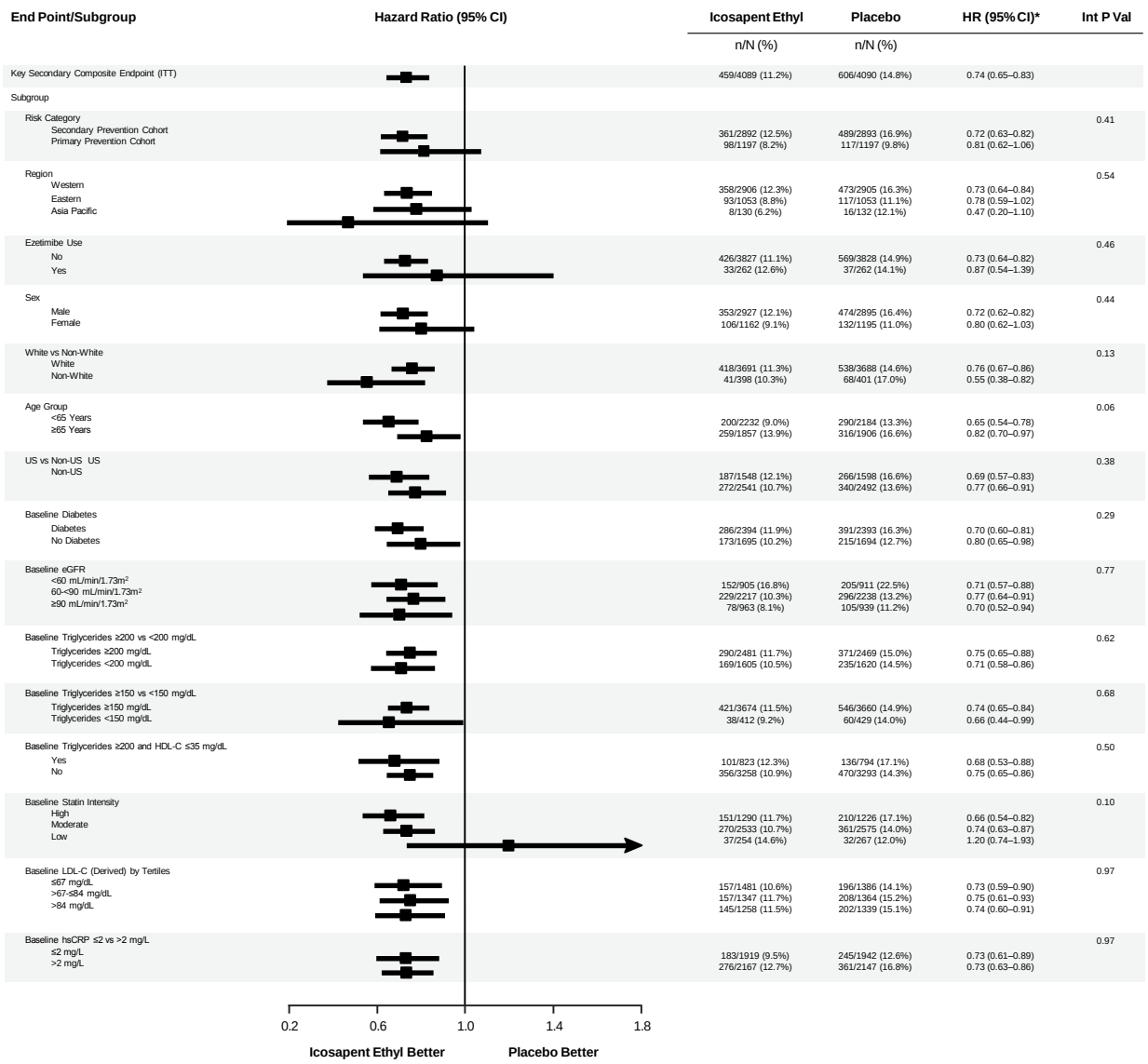
Tertiary / Exploratory Analyses



Bhatt DL, Steg PG, Miller M, et al. N Engl J Med. 2019; 380:11-22.

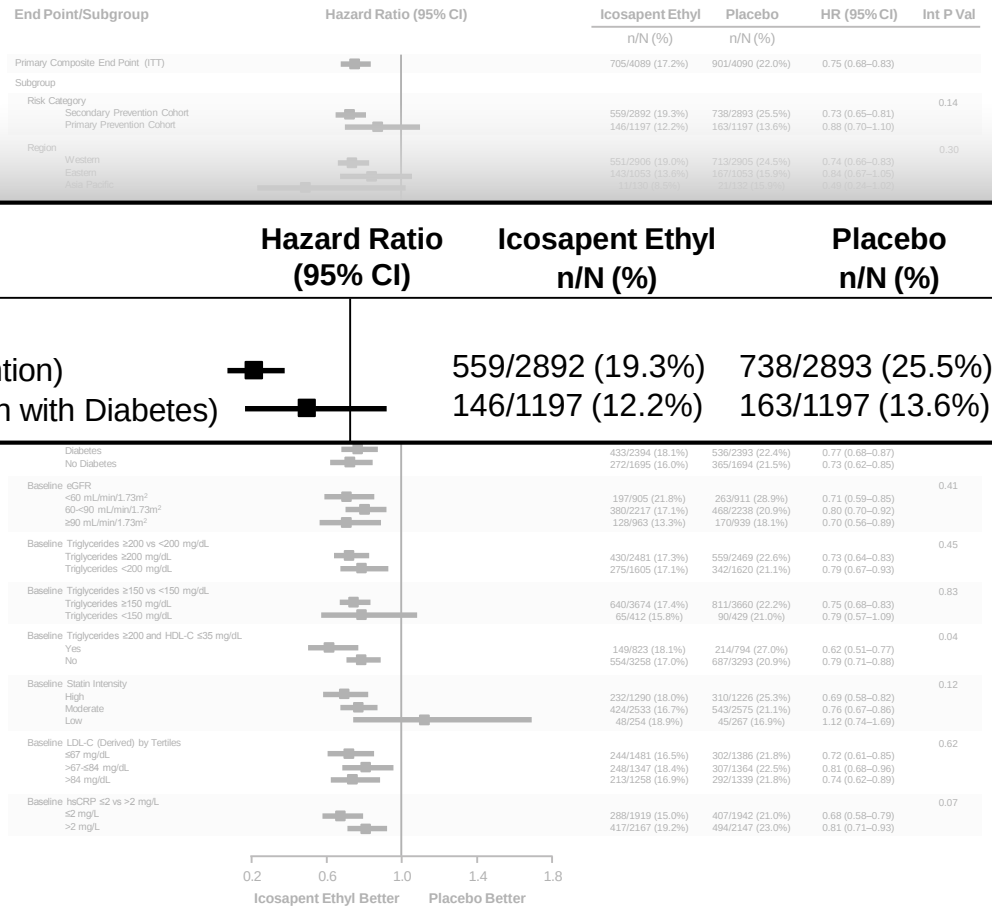
Key Secondary Endpoint: Consistent in Subgroups

Exploratory Analyses



Bhatt DL, Steg PG, Miller M, et al. N Engl J Med. 2019; 380:11-22.

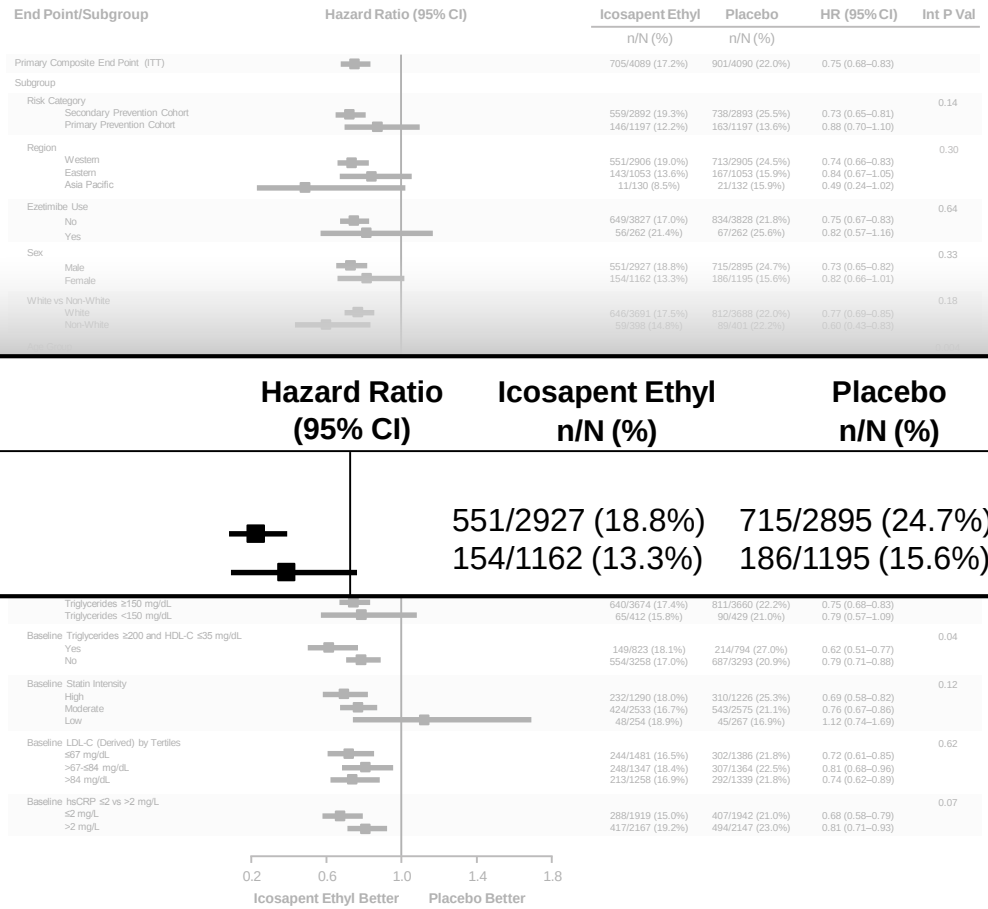
Primary Endpoint: CV Risk Category



Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Risk Category					0.14
CVR1 (Secondary Prevention)		559/2892 (19.3%)	738/2893 (25.5%)	0.73 (0.65–0.81)	
CVR2 (Primary Prevention with Diabetes)		146/1197 (12.2%)	163/1197 (13.6%)	0.88 (0.70–1.10)	

Bhatt DL, Steg PG, Miller M, et al. N Engl J Med. 2019; 380:11-22.

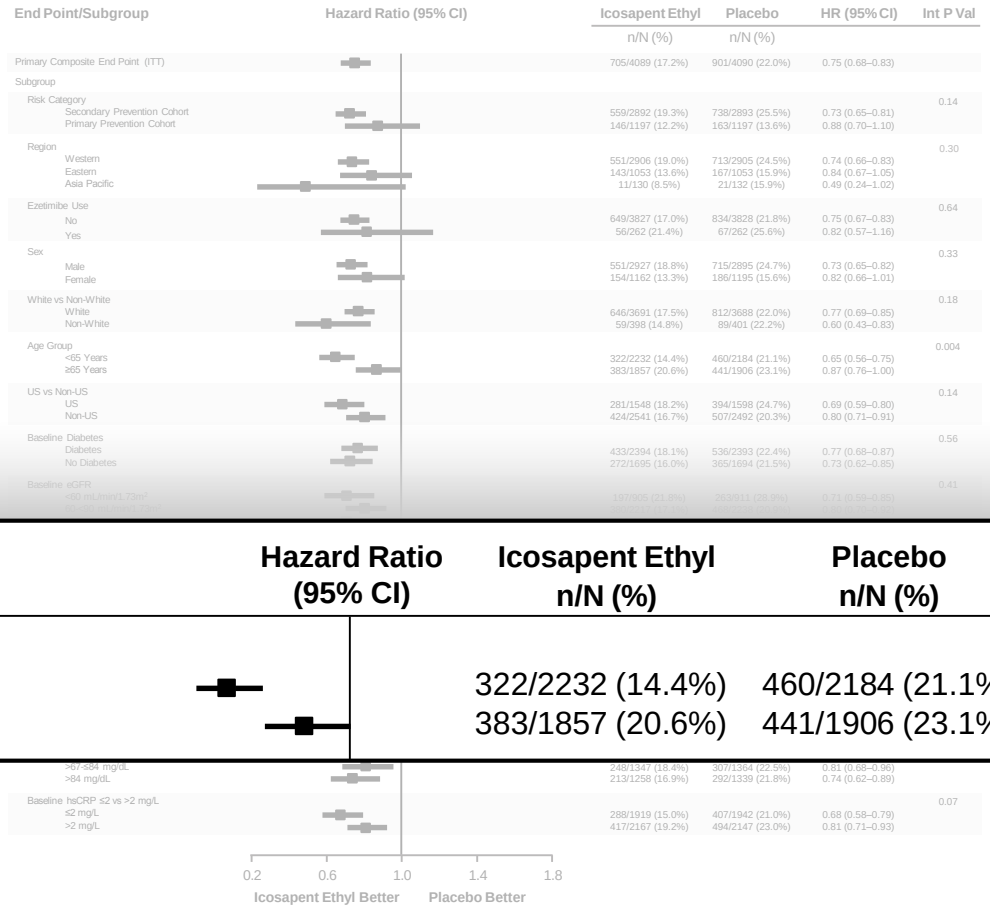
Primary Endpoint: Sex



Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Sex					0.33
Male		551/2927 (18.8%)	715/2895 (24.7%)	0.73 (0.65–0.82)	
Female		154/1162 (13.3%)	186/1195 (15.6%)	0.82 (0.66–1.01)	

Bhatt DL, Steg PG, Miller M, et al. N Engl J Med. 2019; 380:11-22.

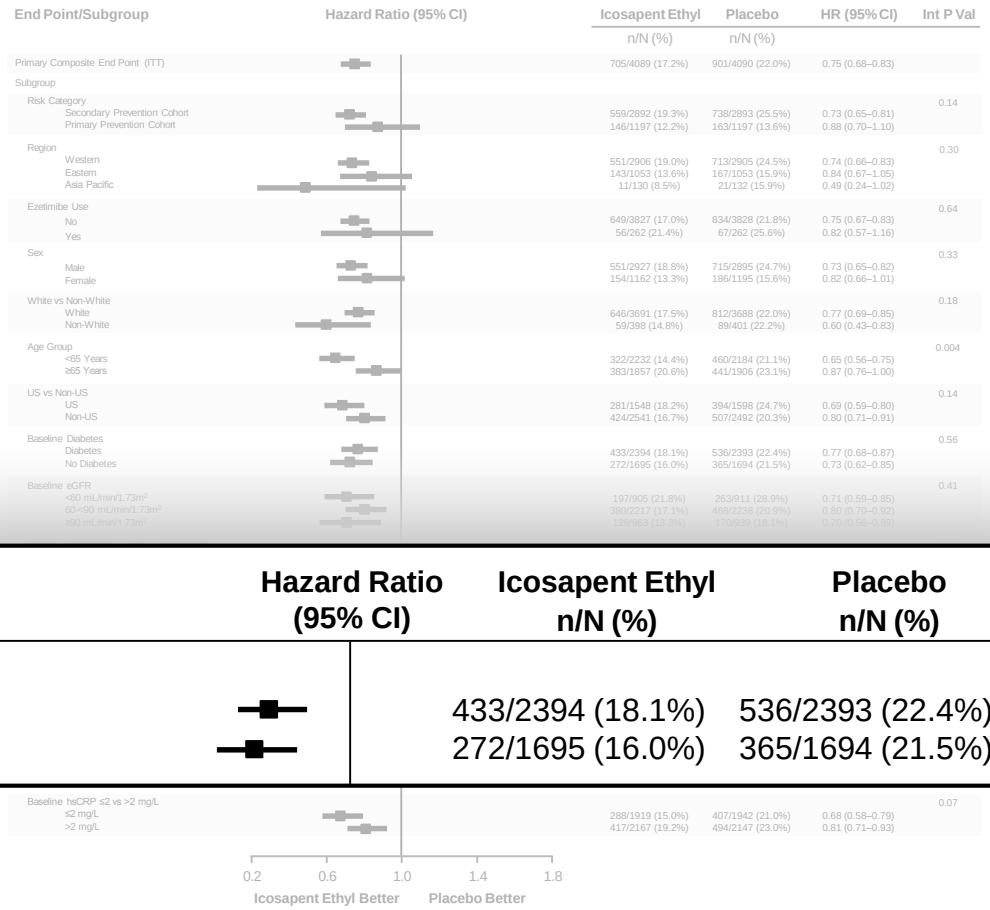
Primary Endpoint: Age Above/Below 65 years



Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Age Group					0.004
<65 Years		322/2232 (14.4%)	460/2184 (21.1%)	0.65 (0.56–0.75)	
≥65 Years		383/1857 (20.6%)	441/1906 (23.1%)	0.87 (0.76–1.00)	

Bhatt DL, Steg PG, Miller M, et al. N Engl J Med. 2019; 380:11-22.
Bhatt DL, Miller M, Brinton EA. et. al. Circulation 2019; DOI: 10.1161/CIRCULATIONAHA.119.044440

Primary Endpoint: Diabetes



Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Baseline Diabetes					0.56
Diabetes		433/2394 (18.1%)	536/2393 (22.4%)	0.77 (0.68–0.87)	
No Diabetes		272/1695 (16.0%)	365/1694 (21.5%)	0.73 (0.62–0.85)	

Bhatt DL, Steg PG, Miller M, et al. N Engl J Med. 2019; 380:11-22.

Primary Endpoint: Baseline TG ≥200 or <200 mg/dL

Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Baseline Triglycerides ≥200 vs <200 mg/dL					0.45
Triglycerides ≥200 mg/dL		430/2481 (17.3%)	559/2469 (22.6%)	0.73 (0.64–0.83)	
Triglycerides <200 mg/dL		275/1605 (17.1%)	342/1620 (21.1%)	0.79 (0.67–0.93)	

Icosapent Ethyl Better Placebo Better

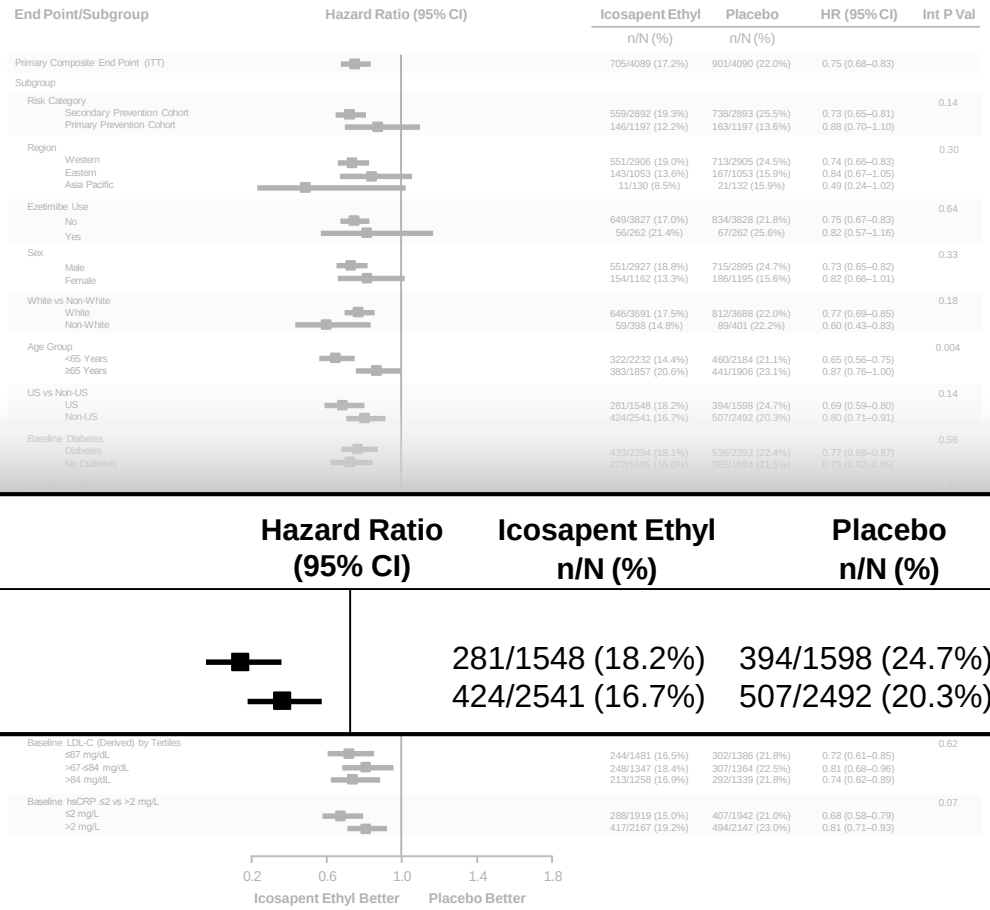
Bhatt DL, Steg PG, Miller M, et al. N Engl J Med. 2019; 380:11-22.

Primary Endpoint: Baseline TG ≥150 or <150 mg/dL

Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Baseline Triglycerides ≥150 vs <150 mg/dL					0.83
Triglycerides ≥150 mg/dL		640/3674 (17.4%)	811/3660 (22.2%)	0.75 (0.68–0.83)	
Triglycerides <150 mg/dL		65/412 (15.8%)	90/429 (21.0%)	0.79 (0.57–1.09)	

Bhatt DL, Steg PG, Miller M, et al. N Engl J Med. 2019; 380:11-22.

Primary Endpoint: US vs. Non-US

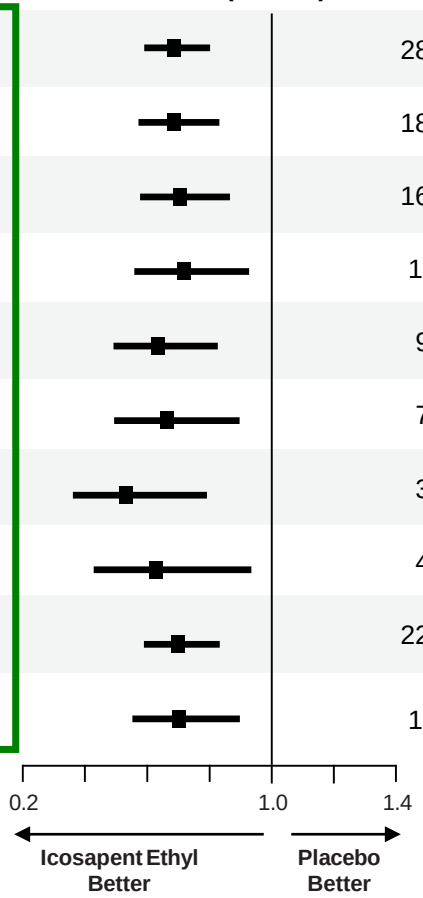


Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
US vs Non-US					0.14
US		281/1548 (18.2%)	394/1598 (24.7%)	0.69 (0.59–0.80)	
Non-US		424/2541 (16.7%)	507/2492 (20.3%)	0.80 (0.71–0.91)	

Bhatt DL, Steg PG, Miller M, et al. N Engl J Med. 2019; 380:11-22.
Bhatt DL, Miller M, Brinton EA. et. al. Circulation 2019; DOI: 10.1161/CIRCULATIONAHA.119.044440

Prespecified Hierarchical Endpoint Testing: USA Subgroup

Endpoint	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	RRR	P-value
Primary Composite (ITT)		281/1548 (18.2%)	394/1598 (24.7%)	0.69 (0.59–0.80)	31%▼	<0.0001
Key Secondary Composite (ITT)		187/1548 (12.1%)	266/1598 (16.6%)	0.69 (0.57–0.83)	31%▼	<0.0001
Cardiovascular Death or Nonfatal Myocardial Infarction		160/1548 (10.3%)	222/1598 (13.9%)	0.71 (0.58–0.86)	29%▼	0.0007
Fatal or Nonfatal Myocardial Infarction		103/1548 (6.7%)	141/1598 (8.8%)	0.72 (0.56–0.93)	28%▼	0.01
Urgent or Emergent Revascularization		94/1548 (6.1%)	144/1598 (9.0%)	0.64 (0.49–0.83)	36%▼	0.0006
Cardiovascular Death		72/1548 (4.7%)	107/1598 (6.7%)	0.66 (0.49–0.90)	34%▼	0.007
Hospitalization for Unstable Angina		38/1548 (2.5%)	71/1598 (4.4%)	0.53 (0.36–0.79)	47%▼	0.002
Fatal or Nonfatal Stroke		41/1548 (2.6%)	65/1598 (4.1%)	0.63 (0.43–0.93)	37%▼	0.02
Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke		221/1548 (14.3%)	309/1598 (19.3%)	0.70 (0.59–0.83)	30%▼	<0.0001
Total Mortality		111/1548 (7.2%)	156/1598 (9.8%)	0.70 (0.55–0.90)	30%▼	0.004



RRR denotes relative risk reduction

Adapted from: Bhatt DL, Miller M, Brinton EA, et al. *Circulation.* 2019.

Reduced Cardiac Arrest & Sudden Cardiac Death

Prespecified Tertiary Endpoints

Type	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	P-value
Cardiac Arrest	22/4089 (0.5%)	42/4090 (1.0%)	0.52 (0.31, 0.86)	0.01
Sudden Cardiac Death	61/4089 (1.5%)	87/4090 (2.1%)	0.69 (0.50, 0.96)	0.03

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019; 380:11-22.

Consistent Results in Revascularization Subtypes

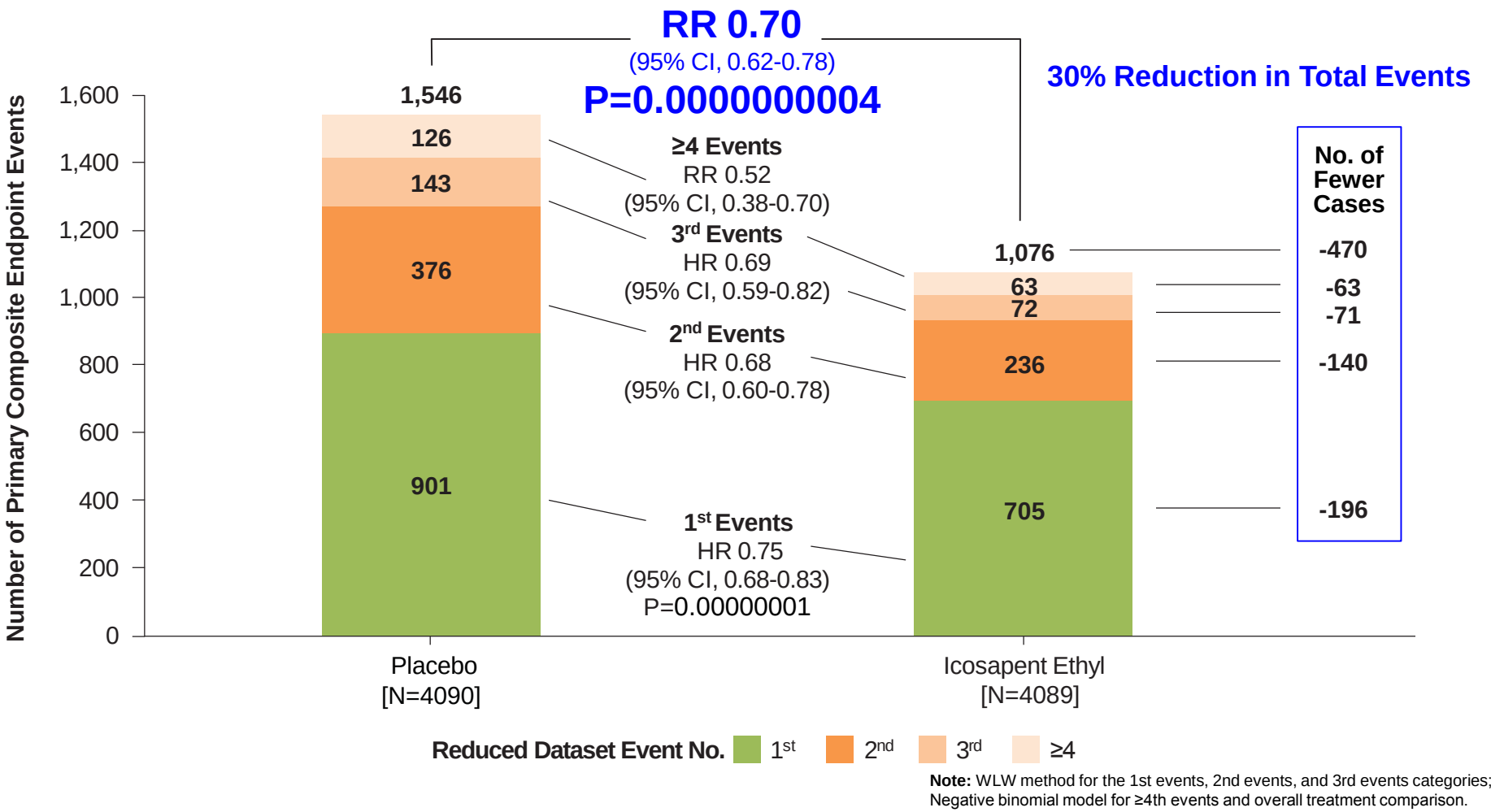
Prespecified Tertiary Endpoints

Type	Icosapent Ethyl (%)	Placebo (%)	Hazard Ratio (95% CI)	P-value
Coronary	9.2%	13.3%	0.66 (0.58, 0.76)	0.0000000008
Emergent	1.0%	1.6%	0.62 (0.42, 0.92)	0.02
Urgent	4.4%	6.6%	0.66 (0.54, 0.79)	0.00001
Elective	4.7%	6.8%	0.68 (0.57, 0.82)	0.00003

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019; 380:11-22.

First and Subsequent Primary Endpoint Events

Prespecified Exploratory Analyses



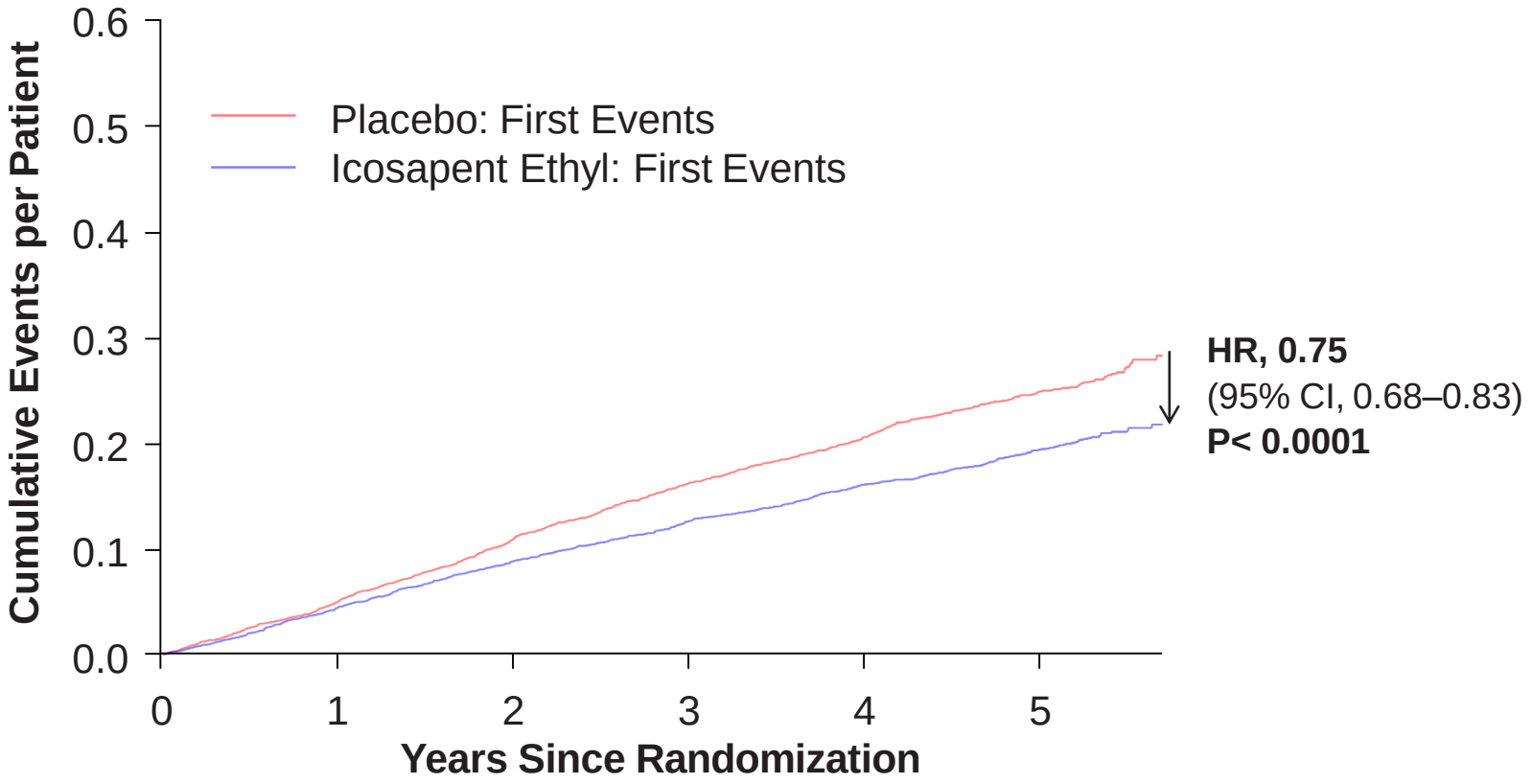
Note: WLW method for the 1st events, 2nd events, and 3rd events categories; Negative binomial model for ≥4th events and overall treatment comparison.

Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019;73:2791-2802.

Primary Endpoint First and Total Event Analysis

Prespecified Exploratory Analyses

Composite MACE: CV death, nonfatal MI, nonfatal stroke, coronary revascularization, unstable angina

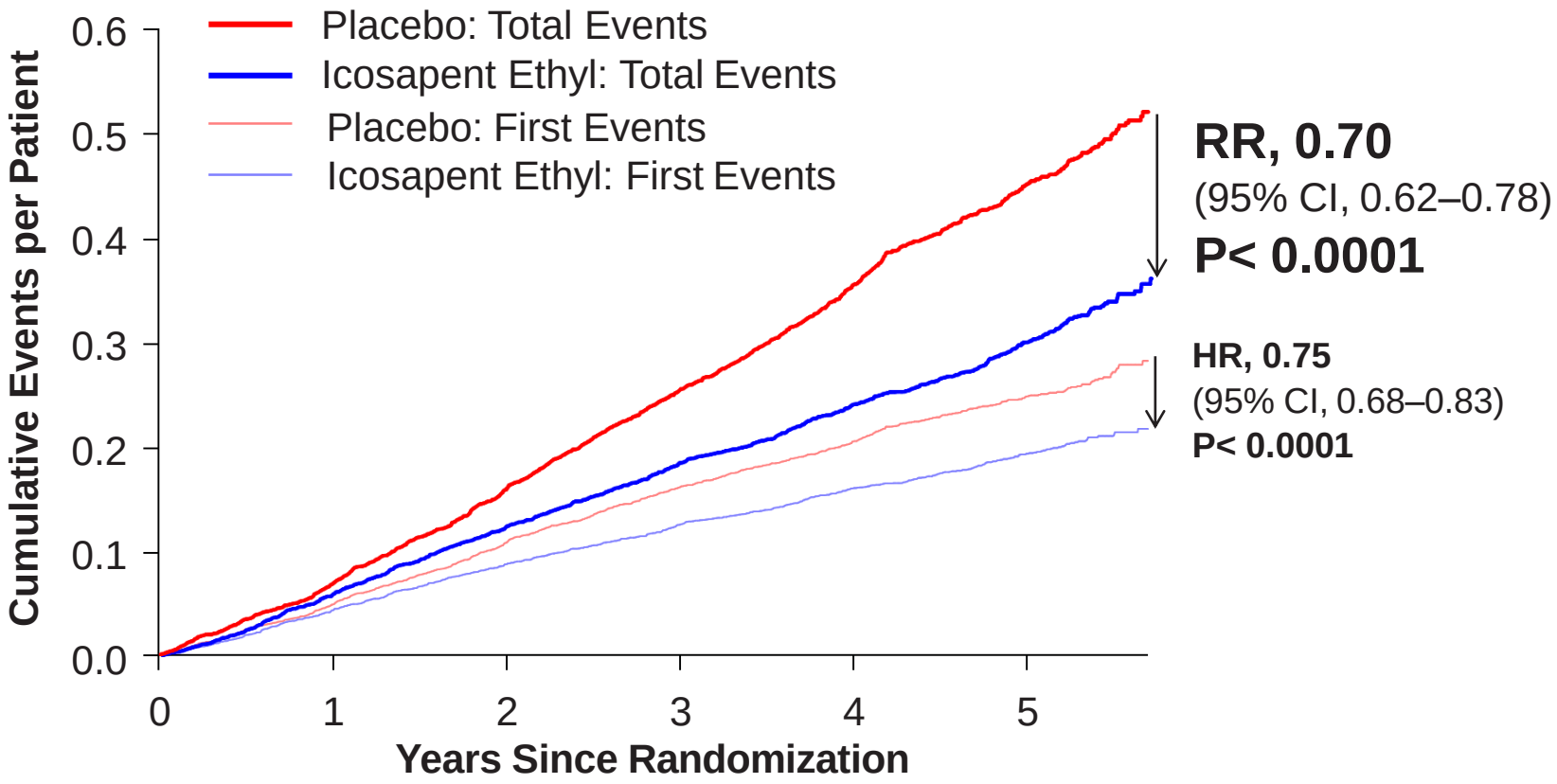


Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019;73:2791-2802.

Primary Endpoint First and Total Event Analysis

Prespecified Exploratory Analyses

Composite MACE: CV death, nonfatal MI, nonfatal stroke, coronary revascularization, unstable angina

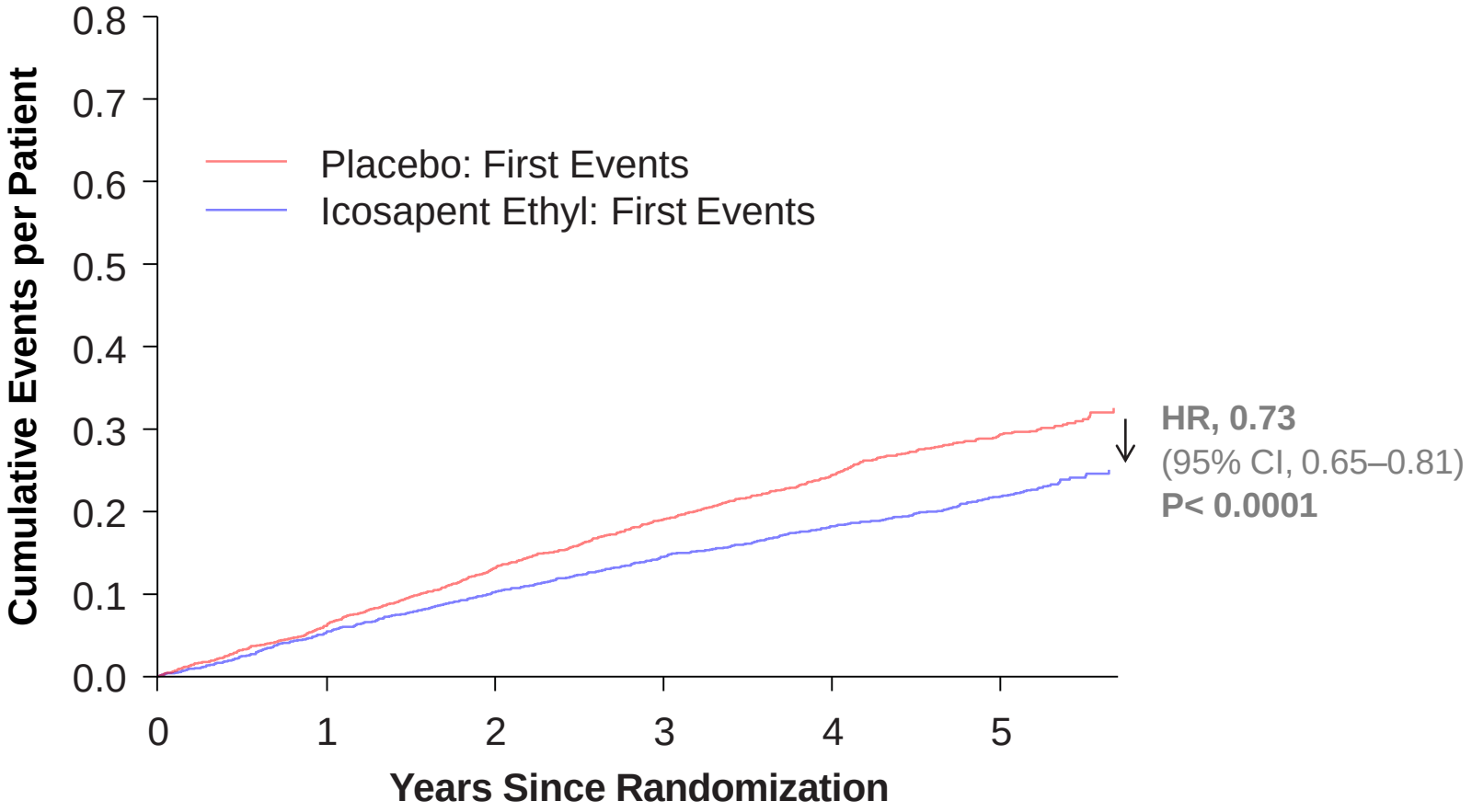


Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019;73:2791-2802.

Primary Endpoint First and Total Event Analysis

CV Risk Cohort 1 (Secondary Prevention)

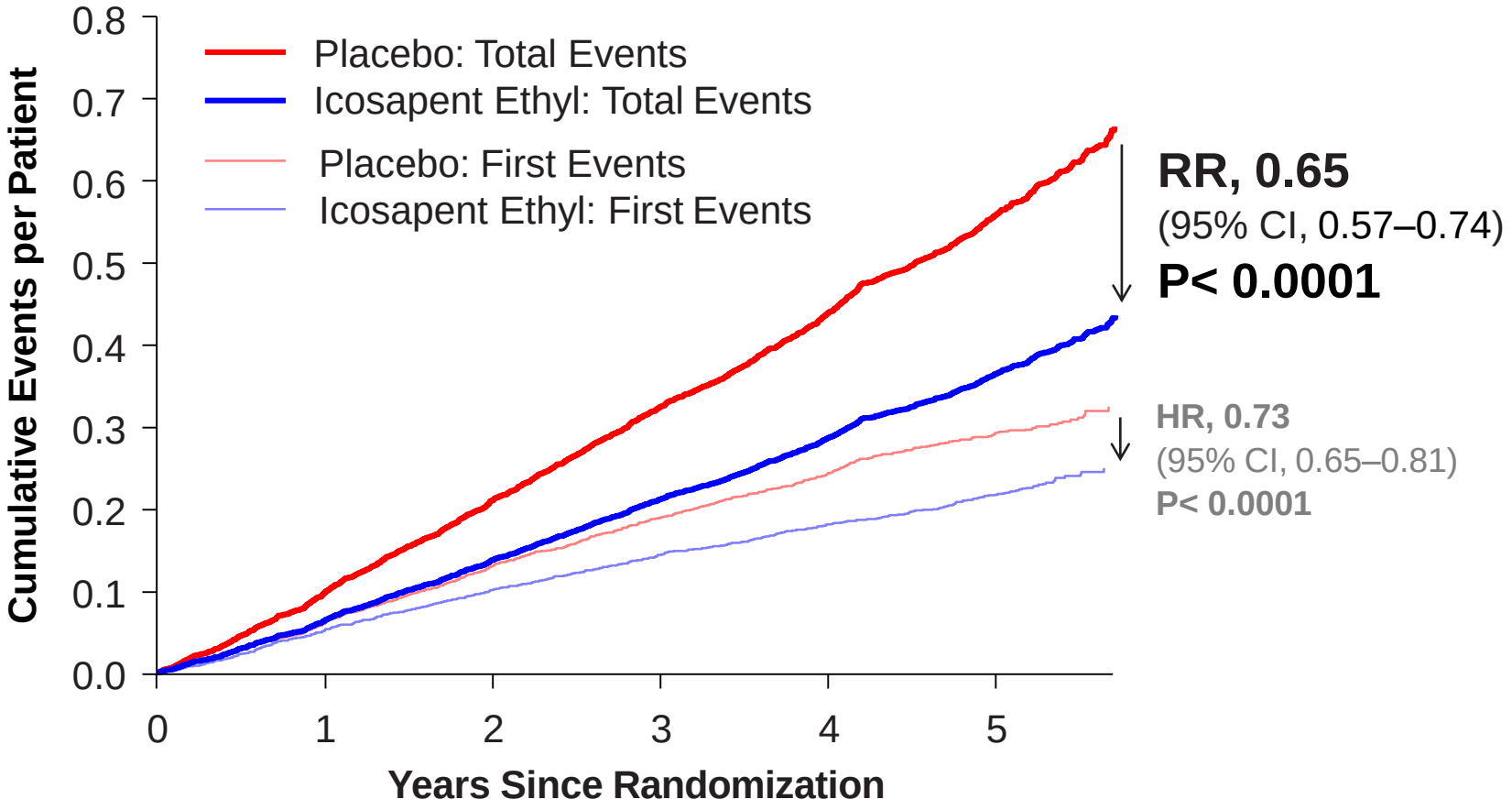
Composite MACE: CV death, nonfatal MI, nonfatal stroke, coronary revascularization, unstable angina



Primary Endpoint First and Total Event Analysis

CV Risk Cohort 1 (Secondary Prevention)

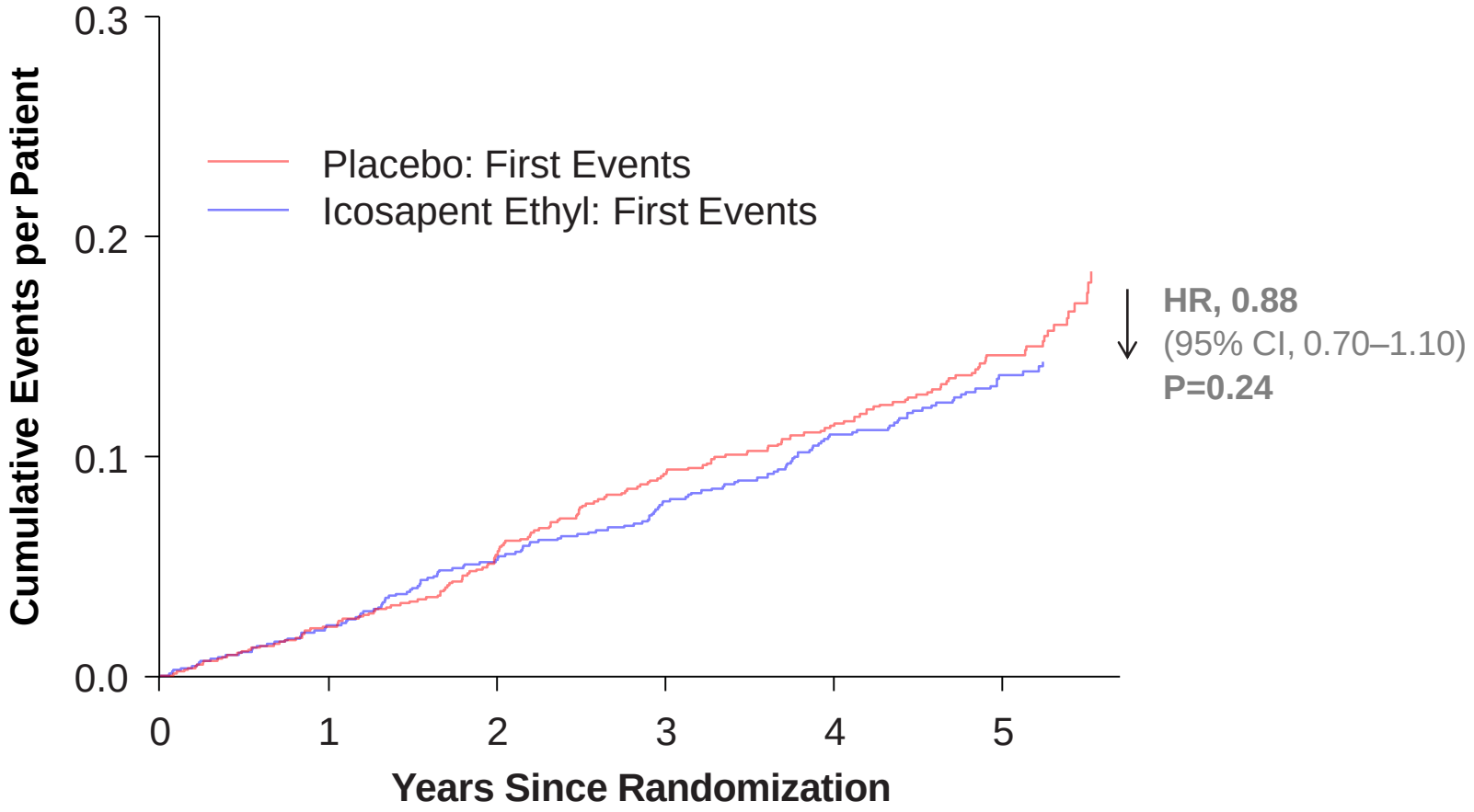
Composite MACE: CV death, nonfatal MI, nonfatal stroke, coronary revascularization, unstable angina



Primary Endpoint First and Total Event Analysis

CV Risk Cohort 2 (High-risk Primary Prevention with Diabetes)

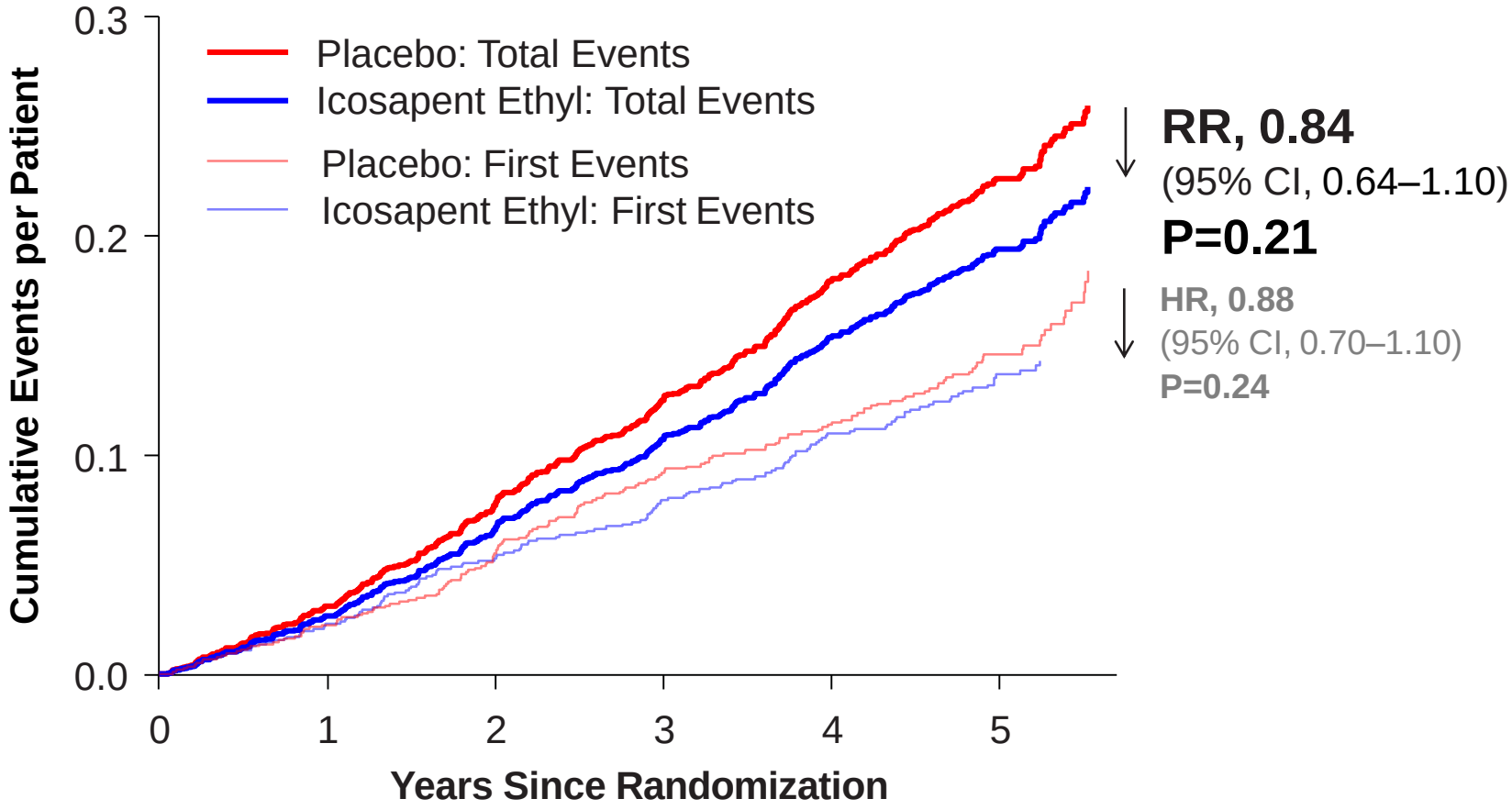
Composite MACE: CV death, nonfatal MI, nonfatal stroke, coronary revascularization, unstable angina



Primary Endpoint First and Total Event Analysis

CV Risk Cohort 2 (High-risk Primary Prevention with Diabetes)

Composite MACE: CV death, nonfatal MI, nonfatal stroke, coronary revascularization, unstable angina

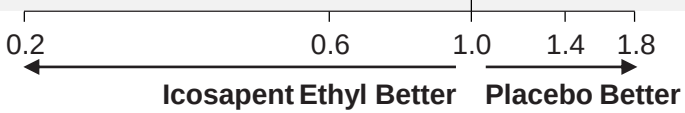


Consistent Effect Across TG Tertiles

Exploratory and Post Hoc Analyses

TIME TO FIRST EVENT:	Icosapent Ethyl	Placebo	HR (95% CI)	P-value
	n/N (%)			
Primary Composite Endpoint (ITT)	705/4089 (17.2)	901/4090 (22.0)	0.75 (0.68–0.83)	<0.0001
Baseline Triglycerides by Tertiles*				
≥81 to ≤190 mg/dL	233/1378 (16.9)	291/1381 (21.1)	0.79 (0.66–0.94)	0.007
>190 to ≤250 mg/dL	246/1370 (18.0)	283/1326 (21.3)	0.80 (0.68–0.95)	0.01
>250 to ≤1401 mg/dL	226/1338 (16.9)	327/1382 (23.7)	0.68 (0.57–0.80)	<0.0001

TOTAL EVENTS:	Icosapent Ethyl	Placebo	RR (95% CI)	P-value
	Rate per 1000 Patient Years			
Primary Composite Endpoint (ITT)	61.1	88.8	0.70 (0.62–0.78)	<0.0001
Baseline Triglycerides by Tertiles**				
≥81 to ≤190 mg/dL	56.4	74.5	0.74 (0.61–0.90)	0.003
>190 to ≤250 mg/dL	63.2	86.8	0.77 (0.63–0.95)	0.01
>250 to ≤1401 mg/dL	64.4	107.4	0.60 (0.50–0.73)	<0.0001



***P (interaction) = 0.33**
****P (interaction) = 0.17**

Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019;74:1159-61.

Biomarker Changes in REDUCE-IT

Limited Sampling Not Intended to Predict Outcomes

	Icosapent Ethyl (N=4089) Median		Placebo (N=4090) Median		Median Between Group Difference at Year 1 *		
Biomarker*	**Baseline**	**Year 1***	**Baseline**	**Year 1**	**Absolute Change from Baseline**	**% Change from Baseline**	**% Change P-value**
EPA (µg/mL)	26.1	144.0	26.1	23.3	+114.9	+385.8	<0.0001
Triglycerides (mg/dL)	216.5	175.0	216.0	221.0	-44.5	-19.7	<0.0001
LDL-C (mg/dL)	74.0	77.0	76.0	84.0	-5.0	-6.6	<0.0001
Non-HDL-C (mg/dL)	118.0	113.0	118.5	130.0	-15.5	-13.1	<0.0001
Apo B (mg/dL)*	82.0	80.0	83.0	89.0	-8.0	-9.7	<0.0001
HDL-C (mg/dL)	40.0	39.0	40.0	42.0	-2.5	-6.3	<0.0001
hsCRP (mg/L)*	2.2	1.8	2.1	2.8	-0.9	-39.9	<0.0001
Log hsCRP (mg/L)	0.8	0.6	0.8	1.0	-0.4	-22.5	<0.0001

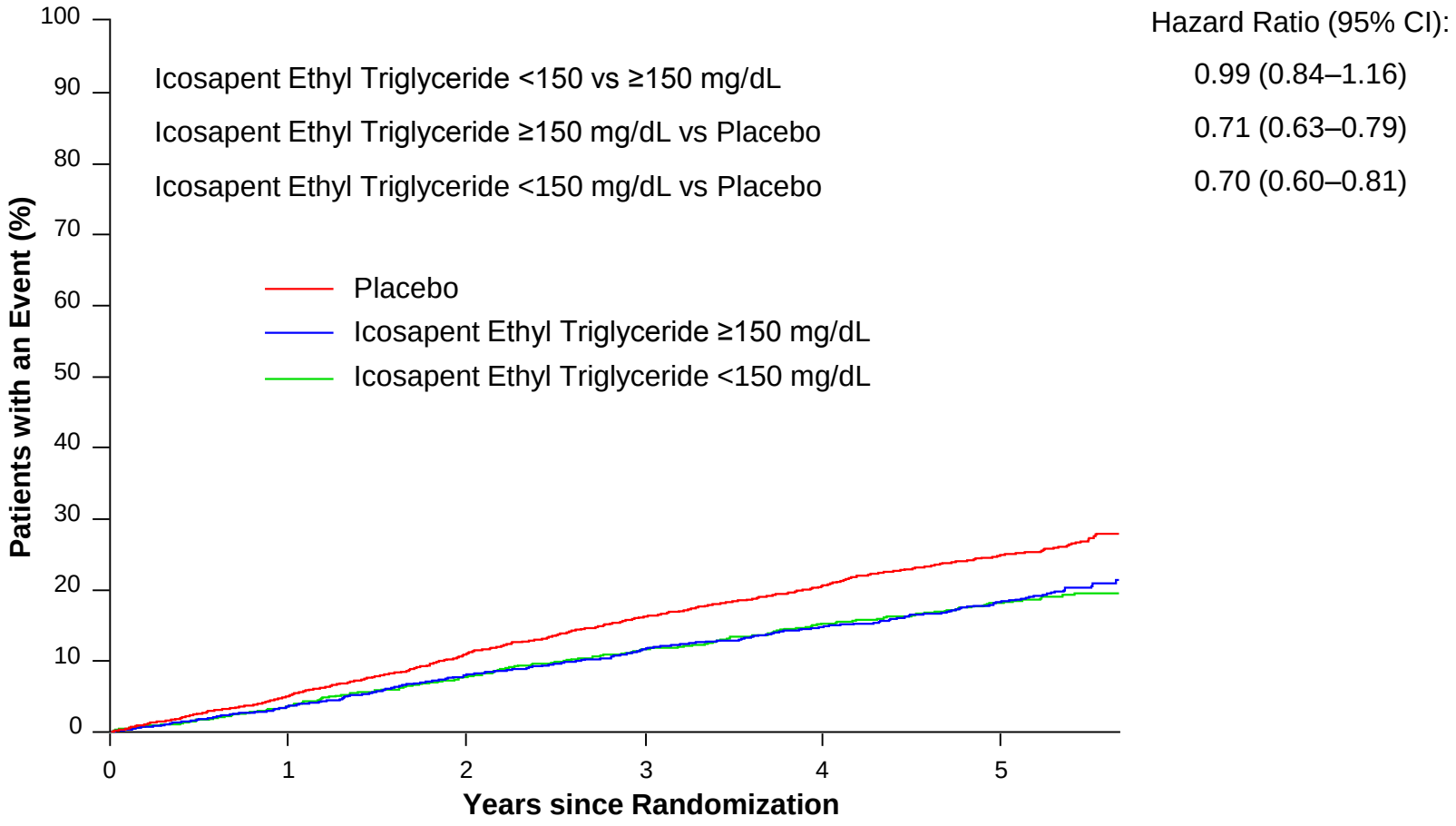
***ApoB and hsCRP were collected at the Year 2 visit.**

Bhatt DL, Steg PG, Miller M, et al. N Engl J Med. 2018;380(1):11-22. doi:10.1056/NEJMoa1812792

On-Treatment TG Did Not Predict Outcome

Tertiary Analysis

Primary End Point by Achieved Triglyceride Level at One Year

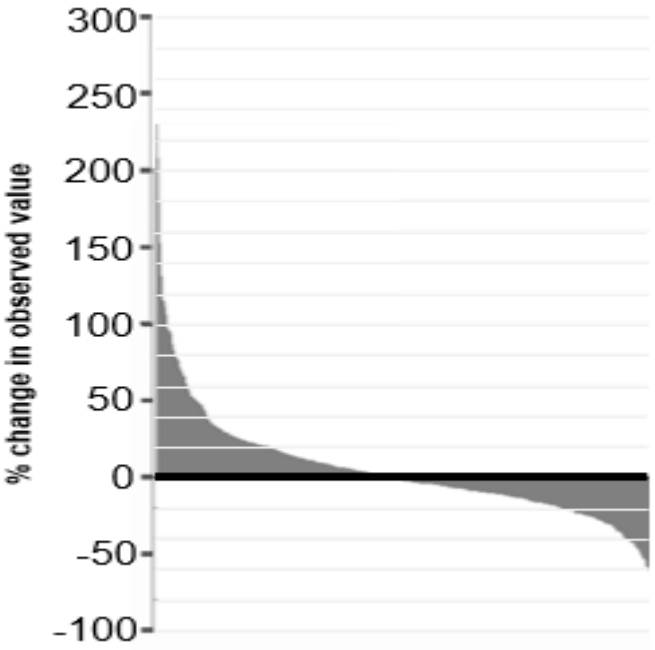


Bhatt DL, Steg PG, Miller M, et al. N Engl J Med. 2019; 380:11-22.

LDL-C Variation Common in Statin-treated Patients

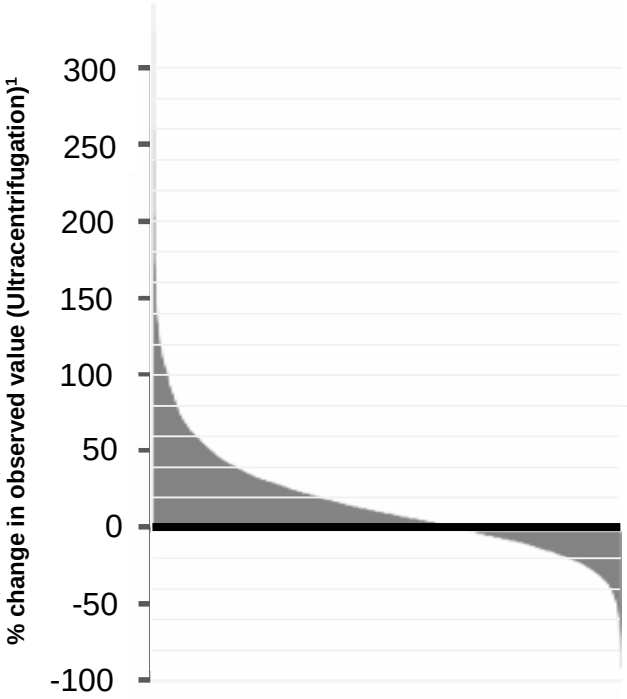
ORION-11 (PCSK9 siRNA)[1]

- 1617 patients
- 95% statin
- Change at 17 months
- Baseline LDL-C = 104–107 mg/dL across treatment groups



REDUCE-IT

- 8179 patients
- Placebo group 100% statin
- Change at 1-yr[2]
- Baseline LDL-C = 76 mg/dL

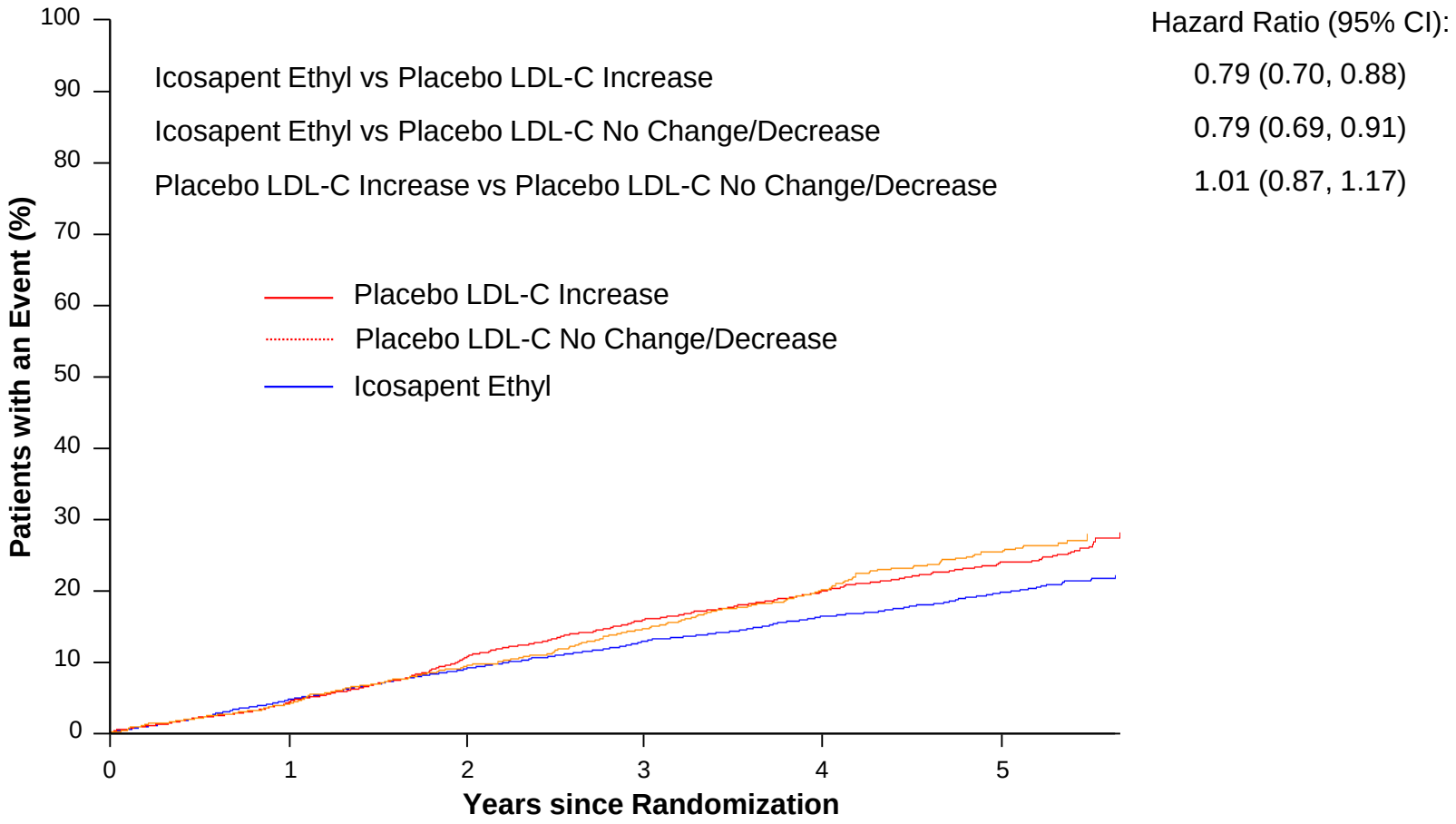


[1] Adapted from: ORION-11: Substantial LDL-C Reduction With Twice Yearly Dosing of Novel Inclisiran. Findings from the Phase 3 ORION-11 study presented by Kausik Kumar Ray, MD, FACC, Sept. 2 at ESC Congress 2019.
[2] Patients with change greater than 400% (3 patients) are excluded

LDL-C Changes Did Not Predict Placebo Outcome

Exploratory Analysis

Primary End Point by Placebo Group LDL-C Change at One Year

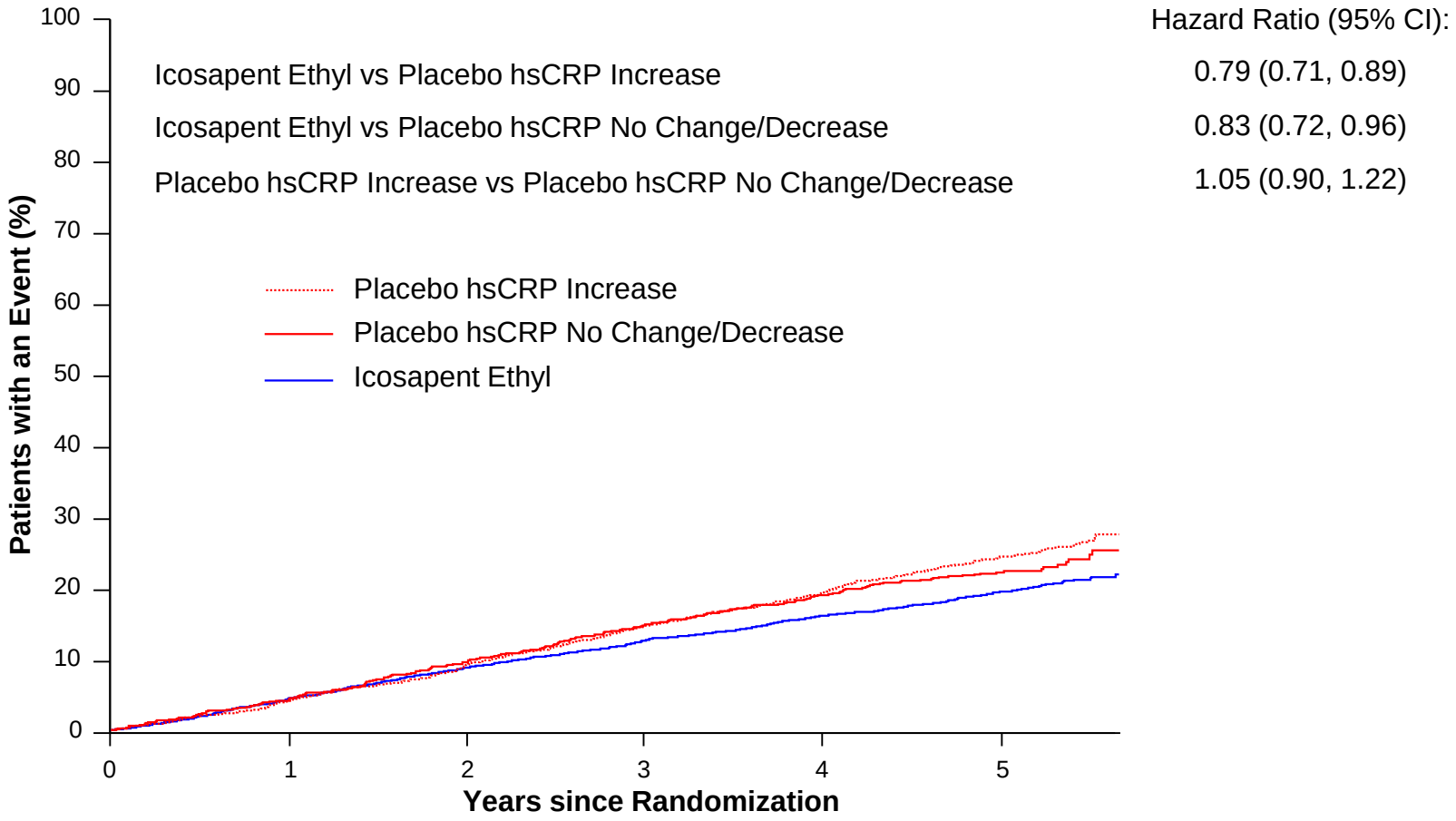


- Per FDA request, the DMC monitored the placebo group and concluded that mineral oil was unlikely to be driving the beneficial effect of icosapent ethyl
- The placebo group event rate consistent with projections and current CVOTs
- Similar analyses conducted for other biomarkers with similar results

hsCRP Change Did Not Predict Placebo Outcome

Exploratory Analysis

Primary End Point by Placebo Group hs-CRP Change at Two Years



Patients with missing Year 2 hs-CRP values were included in the icosapent ethyl arm but excluded from the placebo arm.

Mineral Oil Placebo Analyses

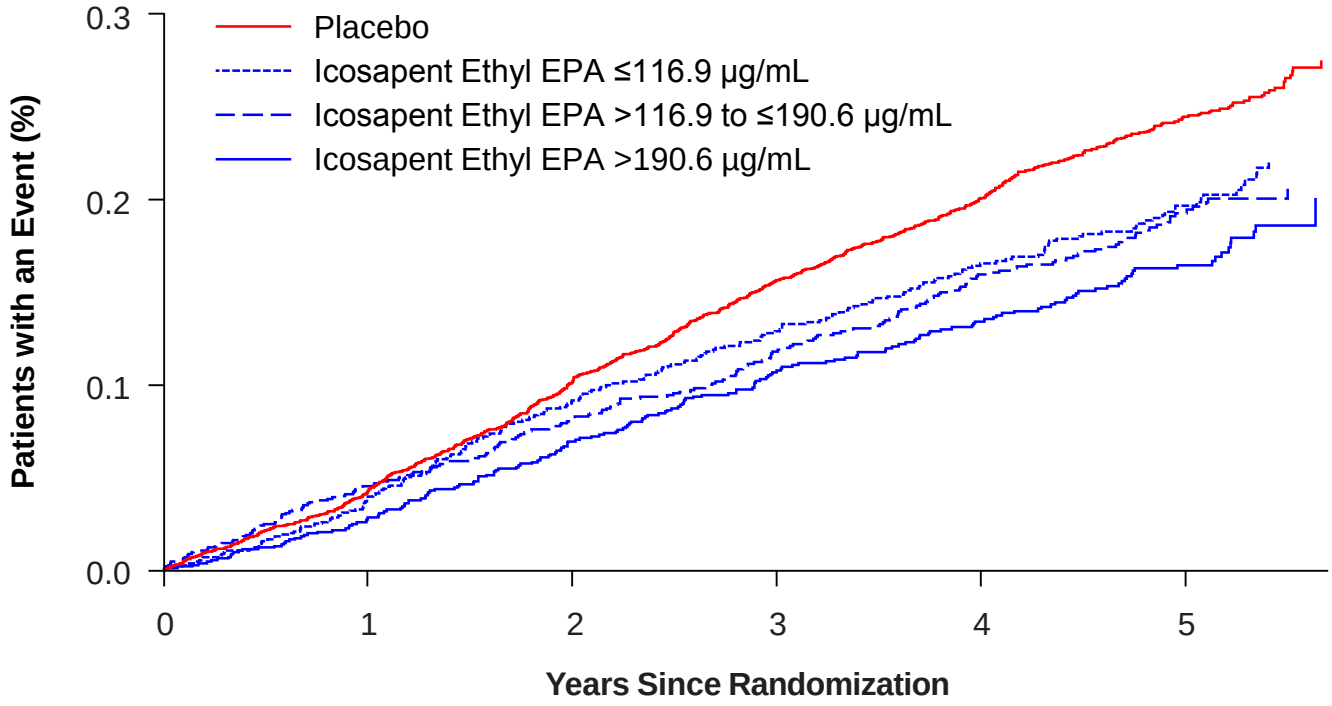
- Amarin and FDA conducted multiple analyses exploring hypothetical effects of mineral oil on statin absorption
  - None alter overall study conclusions
- Amarin analyses show lack of evidence for a mineral oil effect; e.g.,
  - Placebo event rate consistent with comparable historical CVOTs
  - Placebo LDL-C changes consistent with lipid lowering-treatment studies
  - LDL-C changes consistent with some degree of regression to the mean
  - No apparent effect of biomarker increases on placebo group outcomes
  - No clinical evidence of malabsorption
  - No differential LDL-C or outcome effects based on statin type or lipophilicity
- We see no evidence of an effect; any theoretical effect would be minimal
  - Largest LDL-C differential per FDA analyses would translate to a maximal possible impact of approximately 3.1% points of the observed 25% RRR
- Prior trial reported a CV benefit with EPA consistent with REDUCE-IT
  - 19% RRR reported in JELIS, which did not include a placebo

On-Treatment EPA Tertiles Predicted Outcome

Post Hoc Analysis

Primary End Point by Average of EPA Level at Years 1, 2, 3 and End of Study

	Hazard Ratio (95% CI):
Icosapent Ethyl EPA ≤116.9 µg/mL vs Placebo	0.85 (073–0.99)
Icosapent Ethyl EPA >116.9 to ≤190.6 µg/mL vs Placebo	0.74 (0.63–0.86)
Icosapent Ethyl EPA >190.6 µg/mL vs Placebo	0.63 (0.54–0.74)



Efficacy Conclusions

- Icosapent ethyl 4g/day added to statin reduced the primary composite endpoint by 25% over statin alone
- Clinically meaningful, statistically significant CV risk reduction demonstrated
  - Key secondary endpoint reduced by 26%
  - Significant reductions across the prespecified testing hierarchy
  - Each MACE component contributed to the reductions of the primary and key secondary composite endpoints
  - Generally consistent reductions across subgroups
  - Total event analyses for primary composite endpoint showed a reduction of 30%

Bhatt DL, Steg PG, Miller M, et al. N Engl J Med. 2019; 380:11-22.

Review of Safety

Treatment Emergent Adverse Events

No Overall Treatment Difference in Adverse Event Profiles

Preferred Term	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P-value*
Subjects with at Least One TEAE, n (%)	3343 (81.8%)	3326 (81.3%)	0.63
SAE	1252 (30.6%)	1254 (30.7%)	0.98
TEAE Leading to Withdrawal of Study Drug	321 (7.9%)	335 (8.2%)	0.60
SAE Leading to Withdrawal of Study Drug	88 (2.2%)	88 (2.2%)	>0.99
SAE Leading to Death	94 (2.3%)	102 (2.5%)	0.61

TEAE event rates represent the enrolled high CV risk patients and the 4.9-year median study follow-up.
* From Fisher's exact test.

Bhatt DL, Steg PG, Miller M, et al. N Engl J Med. 2019; 380:11-22.

Safety Topics of Interest

- To avoid duplicate counting, clinical events were counted in either Safety or Efficacy analyses, but not in both
  - Both adverse events and positively adjudicated endpoints are presented herein where separate safety and endpoint analyses include related events
- Safety Analyses of Interest
  - Peripheral Edema
    - Only TEAE >6% and higher/statistically significant than placebo
    - No increase in the rate of heart failure in icosapent ethyl patients (HR of 0.95 for CHF; 0.97 for CHF requiring hospitalization)
  - Bleeding
  - Atrial Fibrillation /Flutter

Bhatt DL, Steg PG, Miller M, et al. N Engl J Med. 2019; 380:11-22.

Adverse Events of Interest
Bleeding

	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P-value*
All Bleeding TEAEs	482 (11.8%)	404 (9.9%)	0.006
Bleeding SAEs	111 (2.7%)	85 (2.1%)	0.06
Gastrointestinal bleeding	62 (1.5%)	47 (1.1%)	0.15
Central nervous system bleeding	14 (0.3%)	10 (0.2%)	0.42
Other bleeding	41 (1.0%)	30 (0.7%)	0.19
Intracranial Bleeding	0 (0.0%)	1(0.0%)	>0.99
Hemorrhagic Stroke	13 (0.3%)	10 (0.2%)	0.54

Note: Hemorrhagic stroke was an adjudicated endpoint; other bleeding events were included in Safety analyses

* From Fisher's exact test.

Bhatt DL, Steg PG, Miller M, et al. N Engl J Med. 2019; 380:11-22.

Bleeding Events with Possible Fatal Association
Safety Population

	Icosapent Ethyl (N=4089) n (%)	Placebo (N=4090) n (%)	P-value*
Any Bleeding with a Possible Fatal Association	23 (0.6)	34 (0.8)	0.18
Likely Contributing to a Fatal Event	20 (0.5)	23 (0.6)	0.76

Note: Identification of patients with a fatal event possibly associated with a bleeding event was conducted through exhaustive search of the clinical adverse events dataset and the Clinical Endpoint Committee (CEC) endpoint database, as well as through comprehensive Sponsor medical review of the relevant data/source documents. Includes TEAEs and positively adjudicated hemorrhagic stroke.

* From Fisher's exact test.

None of the 57 deaths presented were assessed as causally related to study drug in either group, per Investigator assessment; one bleeding event preceding the death in each treatment group was considered possibly related to study drug per Investigator assessment.

Adverse Events of Interest: All Bleeding
By Baseline Medications of Interest

Antithrombotic therapy (at baseline)	Patients with bleeding/ at risk %		
	Icosapent Ethyl n/N (%)	Placebo n/N (%)	P-value*
All Randomized Patients	482/4089 (11.8)	404/4090 (9.9)	0.006
No Antithrombotics	45/584 (7.7)	42/601 (7.0)	0.66
One Antiplatelet	269/2416 (11.1)	234/2408 (9.7)	0.11
Two or More Antiplatelets	120/841 (14.3)	87/828 (10.5)	0.02
Anticoagulant	81/385 (21.0)	64/390 (16.4)	0.12
Single Antiplatelet Plus Anticoagulant	26/114 (22.8)	21/123 (17.1)	0.33

Note: n is the number of patients with treatment emergent adverse events of bleeding; N is the total number of subjects within each medication category.
*From Fisher's exact test.

Source: Table 14.2.13.2

Adverse Events of Interest: Serious Bleeding
By Baseline Medications of Interest

Antithrombotic therapy (at baseline)	Patients with bleeding/ at risk %		
	Icosapent Ethyl n/N (%)	Placebo n/N (%)	P-value*
All Randomized Patients	111/4089 (2.7)	85/4090 (2.1)	0.06
No Antithrombotics	8/584 (1.4)	6/601 (1.0)	0.60
One Antiplatelet	58/2416 (2.4)	43/2408 (1.8)	0.16
Two or More Antiplatelets	31/841 (3.7)	19/828 (2.3)	0.11
Anticoagulant	27/385 (7.0)	27/390 (6.9)	>0.99
Single Antiplatelet Plus Anticoagulant	8/114 (7.0)	8/123 (6.5)	>0.99

Note: n is the number of patients with treatment emergent adverse events of bleeding; N is the total number of subjects within each medication category.
*From Fisher's exact test.

Source: Table 14.2.13.2

Adverse Events of Interest: All Bleeding
By On-study Medications of Interest

Antithrombotic therapy (on treatment)	Patients with bleeding/ at risk %		
	Icosapent Ethyl n/N (%)	Placebo n/N (%)	P-value*
All Randomized Patients	482/4089 (11.8)	404/4090 (9.9)	0.006
No Antithrombotics	22/449 (4.9)	22/445 (4.8)	>0.99
One Antiplatelet	216/2166 (10.0)	174/2098 (8.3)	0.06
Two or More Antiplatelets	199/1241 (16.0)	175/1319 (13.3)	0.05
Anticoagulant	230/989 (23.3)	195/1009 (19.3)	0.03
Single Antiplatelet Plus Anticoagulant	89/401 (22.2)	76/396 (19.2)	0.34

Note: n is the number of patients with treatment emergent adverse events of bleeding; N is the total number of subjects within each medication category.
*From Fisher's exact test.

Source: Table 14.2.13.2

Adverse Events of Interest: Serious Bleeding
By On-study Medications of Interest

Antithrombotic therapy (on treatment)	Patients with bleeding/ at risk %		
	Icosapent Ethyl n/N (%)	Placebo n/N (%)	P-value*
All Randomized Patients	111/4089 (2.7)	85/4090 (2.1)	0.06
No Antithrombotics	1/449 (0.2)	1/445 (0.2)	>0.99
One Antiplatelet	41/2166 (1.9)	32/2098 (1.5)	0.41
Two or More Antiplatelets	55/1241 (4.4)	40/1319 (3.0)	0.07
Anticoagulant	63/989 (6.4)	58/1009 (5.7)	0.57
Single Antiplatelet Plus Anticoagulant	20/401 (5.0)	19/396 (4.8)	>0.99

Note: n is the number of patients with treatment emergent adverse events of bleeding; N is the total number of subjects within each medication category.
*From Fisher's exact test.

Source: Table 14.2.13.2

Adverse Events of Interest: All Bleeding
Secondary Prevention and High-risk Primary Prevention

CVR1 (Secondary Prevention)	Icosapent Ethyl (N=2892)	Placebo (N=2893)	P-value[2]
Bleeding Related Disorders[1]	347 (12.0%)	292 (10.1%)	0.02
Gastrointestinal Bleeding	89 (3.1%)	82 (2.8%)	0.59
CNS Bleeding	17 (0.6%)	9 (0.3%)	0.12
Other Bleeding	255 (8.8%)	220 (7.6%)	0.09
Hemorrhagic Stroke*	13 (0.4%)	8 (0.3%)	0.29
Bleeding Likely Contributing to Fatal Event	18 (0.6%)	17 (0.6%)	0.87

CVR2 (High-risk Primary Prevention with Diabetes)	(N=1197)	(N=1197)	
Bleeding Related Disorders[1]	147 (12.3%)	120 (10.0%)	0.09
Gastrointestinal Bleeding	38 (3.2%)	34 (2.8%)	0.72
CNS Bleeding	3 (0.3%)	3 (0.3%)	>0.99
Other Bleeding	121 (10.1%)	92 (7.7%)	0.04
Hemorrhagic Stroke*	0	2 (0.2%)	0.50
Bleeding Likely Contributing to Fatal Event	2 (0.2%)	6 (0.5%)	0.29

* Hemorrhagic stroke was an adjudicated endpoint; other bleeding events were included in Safety analyses
1 Bleeding-related disorders are identified by the SMQs of "Gastrointestinal haemorrhage," "Central Nervous System haemorrhages and cerebrovascular conditions," and "Haemorrhage terms (excl laboratory terms)."
2 Fishers Exact test.

Adverse Events of Interest: Serious Bleeding
Secondary Prevention and High-risk Primary Prevention

CVR1 (Secondary Prevention)	Icosapent Ethyl (N=2892)	Placebo (N=2893)	P-value[2]
Serious Bleeding Related Disorders[1]	92 (3.2%)	69 (2.4%)	0.07
Gastrointestinal Bleeding	43 (1.5%)	35 (1.2%)	0.36
CNS Bleeding	12 (0.4%)	7 (0.2%)	0.26
Other Bleeding	29 (1.0%)	21 (0.7%)	0.26
Hemorrhagic Stroke*	13 (0.4%)	8 (0.3%)	0.29
Bleeding Likely Contributing to Fatal Event	18 (0.6%)	17 (0.6%)	0.87

CVR2 (High-risk Primary Prevention with Diabetes)	(N=1197)	(N=1197)	
Serious Bleeding Related Disorders[1]	31 (2.6%)	26 (2.2%)	0.59
Gastrointestinal Bleeding	19 (1.6%)	12 (1.0%)	0.28
CNS Bleeding	2 (0.2%)	3 (0.3%)	>0.99
Other Bleeding	12 (1.0%)	9 (0.8%)	0.66
Hemorrhagic Stroke*	0	2 (0.2%)	0.50
Bleeding Likely Contributing to Fatal Event	2 (0.2%)	6 (0.5%)	0.29

* Hemorrhagic stroke was an adjudicated endpoint; other bleeding events were included in Safety analyses
1 Bleeding-related disorders are identified by the SMQs of "Gastrointestinal haemorrhage," "Central Nervous System haemorrhages and cerebrovascular conditions," and "Haemorrhage terms (excl laboratory terms)."
2 Fishers Exact test.

Atrial Fibrillation / Flutter

- Atrial fibrillation/flutter requiring hospitalization ≥24 hours was an adjudicated efficacy endpoint
- All other atrial fibrillation/flutter events reside in the safety database

	Icosapent Ethyl (N=4089) n (%)	Placebo (N=4090) n (%)	P-value*
Afib/Aflutter TEAEs and positively adjudicated Afib/Aflutter requiring ≥24 hours hospitalization	321 (7.9)	248 (6.1)	0.002
Afib/Aflutter TEAEs[1]	236 (5.8)	183 (4.5)	0.008
Serious Afib/Aflutter TEAEs[2]	22 (0.5)	20 (0.5)	0.76
Positively adjudicated Afib/Aflutter requiring ≥24 hours hospitalization[3]	127 (3.1)	84 (2.1)	0.004

Note: Clinical consequences, including stroke, MI, cardiac arrest, and sudden cardiac death were reduced in the overall ITT population, with consistent results in those with a history of atrial fibrillation at baseline.

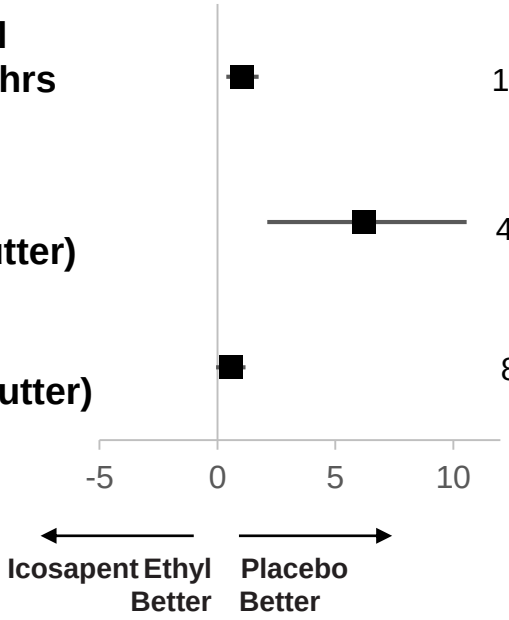
* From Fisher's exact test.

1. Includes atrial fibrillation/flutter TEAEs. 2. Includes a subset of atrial fibrillation/flutter AEs meeting seriousness criteria. 3. Includes positively adjudicated atrial fibrillation/flutter requiring ≥24 hours hospitalization clinical events by the Clinical Endpoint Committee.

Atrial Fibrillation / Flutter Requiring ≥ 24 Hrs Hosp.

by Baseline Atrial Fib/Flutter – ITT

	ARD (95% CI)	Icosapent Ethyl	Placebo	ARD (95% CI)	P-value
		n/N (%)	n/N (%)		
Atrial Fibrillation/Atrial Flutter Requiring ≥ 24 hrs Hospitalization		127/4089 (3.1%)	84/4090 (2.1%)	1.05 (0.37, 1.75)	0.003
Yes (i.e., Recurrent Afib/flutter)		46/ 368 (12.5%)	24/ 383 (6.3%)	6.23 (2.11, 10.56)	0.003
No (i.e., New Onset Afib/flutter)		81/3721 (2.2%)	60/3707 (1.6%)	0.56 (-0.06, 1.19)	0.08

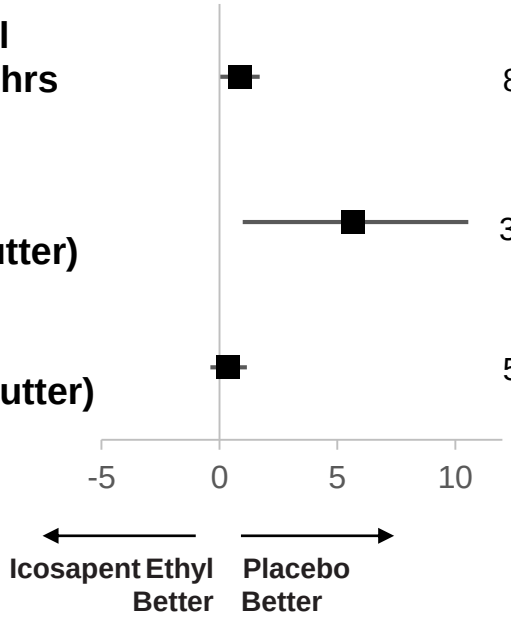


Source: Table 14.2.6.40.1

Atrial Fibrillation / Flutter Requiring ≥ 24 Hrs Hosp.

by Baseline Atrial Fib/Flutter – Secondary Prevention

	ARD (95% CI)	Icosapent Ethyl	Placebo	ARD (95% CI)	P-value
		n/N (%)	n/N (%)		
Atrial Fibrillation/Atrial Flutter Requiring ≥ 24 hrs Hospitalization		89/2892 (3.1%)	64/2893 (2.2%)	0.87 (0.04, 1.71)	0.04
Yes (i.e., Recurrent Afib/flutter)		31/ 272 (11.4%)	16/ 278 (5.8%)	5.64 (0.99, 10.55)	0.02
No (i.e., New Onset Afib/flutter)		58/2620 (2.2%)	48/2615 (1.8%)	0.38 (-0.39, 1.16)	0.33

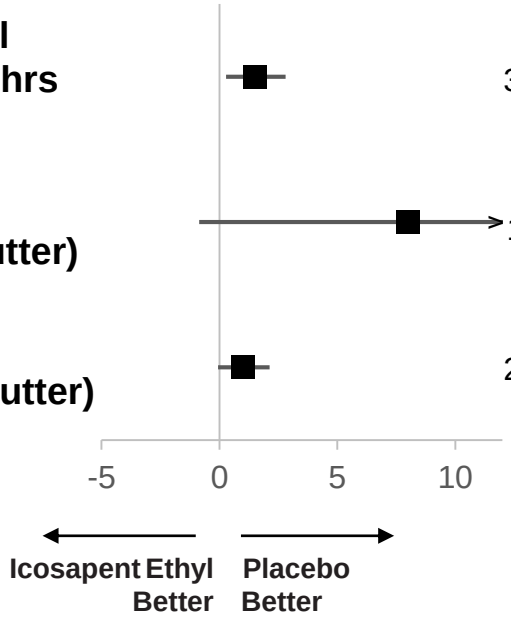


Source: Figure 14.205.1.1

Atrial Fibrillation / Flutter Requiring ≥ 24 Hrs Hosp.

by Baseline Atrial Fib/Flutter – High-risk Primary Prevention

	ARD (95% CI)	Icosapent Ethyl	Placebo	ARD (95% CI)	P-value
		n/N (%)	n/N (%)		
Atrial Fibrillation/Atrial Flutter Requiring ≥ 24 hrs Hospitalization		38/1197 (3.2%)	20/1197 (1.7%)	1.50 (0.28, 2.81)	0.02
Yes (i.e., Recurrent Afib/flutter)		15/ 96 (15.6%)	8/ 105 (7.6%)	8.01 (-0.86, 17.54)	0.08
No (i.e., New Onset Afib/flutter)		23/1101 (2.1%)	12/1092 (1.1%)	0.99 (-0.06, 2.13)	0.06



Source: Figure 14.205.1.2

Endpoints by History of Atrial Fibrillation/Flutter

ITT Population

	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	pVal	Int pVal
Primary Composite Endpoint	705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68, 0.83)	<0.0001	
Atrial Fibrillation/Flutter-Yes	87/ 368 (23.6%)	98/ 383 (25.6%)	0.87 (0.65, 1.17)	0.36	0.37
Atrial Fibrillation/Flutter-No	618/3721 (16.6%)	803/3707 (21.7%)	0.74 (0.67, 0.82)	<0.0001	
Key Secondary Composite Endpoint	459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65, 0.83)	<0.0001	
Atrial Fibrillation/Flutter-Yes	64/ 368 (17.4%)	75/ 383 (19.6%)	0.81 (0.58, 1.14)	0.23	0.55
Atrial Fibrillation/Flutter-No	395/3721 (10.6%)	531/3707 (14.3%)	0.72 (0.64, 0.82)	<0.0001	
CV Death	174/4089 (4.3%)	213/4090 (5.2%)	0.80 (0.66, 0.98)	0.03	
Atrial Fibrillation/Flutter-Yes	30/ 368 (8.2%)	36/ 383 (9.4%)	0.81 (0.50, 1.31)	0.38	0.99
Atrial Fibrillation/Flutter-No	144/3721 (3.9%)	177/3707 (4.8%)	0.80 (0.64, 1.00)	0.05	
Nonfatal MI	237/4089 (5.8%)	332/4090 (8.1%)	0.70 (0.59, 0.82)	<0.0001	
Atrial Fibrillation/Flutter-Yes	25/ 368 (6.8%)	25/ 383 (6.5%)	0.95 (0.55, 1.66)	0.87	0.25
Atrial Fibrillation/Flutter-No	212/3721 (5.7%)	307/3707 (8.3%)	0.68 (0.57, 0.81)	<0.0001	
Nonfatal Stroke	85/4089 (2.1%)	118/4090 (2.9%)	0.71 (0.54, 0.94)	0.01	
Atrial Fibrillation/Flutter-Yes	15/ 368 (4.1%)	24/ 383 (6.3%)	0.60 (0.31, 1.14)	0.12	0.58
Atrial Fibrillation/Flutter-No	70/3721 (1.9%)	94/3707 (2.5%)	0.73 (0.54, 1.00)	0.05	
Coronary Revascularization	376/4089 (9.2%)	544/4090 (13.3%)	0.66 (0.58, 0.76)	<0.0001	
Atrial Fibrillation/Flutter-Yes	38/ 368 (10.3%)	40/ 383 (10.4%)	0.95 (0.61, 1.48)	0.81	0.12
Atrial Fibrillation/Flutter-No	338/3721 (9.1%)	504/3707 (13.6%)	0.64 (0.56, 0.74)	<0.0001	
Hospitalization for Unstable Angina	108/4089 (2.6%)	157/4090 (3.8%)	0.68 (0.53, 0.87)	0.002	
Atrial Fibrillation/Flutter-Yes	9/ 368 (2.4%)	9/ 383 (2.3%)	1.04 (0.41, 2.64)	0.93	0.42
Atrial Fibrillation/Flutter-No	99/3721 (2.7%)	148/3707 (4.0%)	0.66 (0.51, 0.85)	0.001	
Total Mortality	274/4089 (6.7%)	310/4090 (7.6%)	0.87 (0.74, 1.02)	0.09	
Atrial Fibrillation/Flutter-Yes	47/ 368 (12.8%)	57/ 383 (14.9%)	0.79 (0.53, 1.16)	0.22	0.60
Atrial Fibrillation/Flutter-No	227/3721 (6.1%)	253/3707 (6.8%)	0.88 (0.74, 1.06)	0.18	

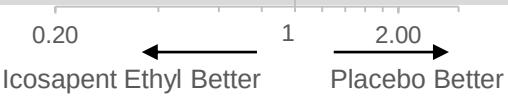


Figure 14.2.105.5.BB

Abbreviations: CI = confidence interval; HR = hazard ratio; Int = interaction; ITT = Intent-to-Treat; pVal = p-value.

Endpoints by On-Study Atrial Fibrillation/Flutter

ITT Population

	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	pVal	Int pVal
Primary Composite Endpoint	705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68, 0.83)	<0.0001	
Atrial Fibrillation/Flutter-Yes	102/ 321 (31.8%)	93/ 248 (37.5%)	0.84 (0.63, 1.12)	0.24	0.37
Atrial Fibrillation/Flutter-No	603/3768 (16.0%)	808/3842 (21.0%)	0.73 (0.66, 0.81)	<0.0001	
Key Secondary Composite Endpoint	459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65, 0.83)	<0.0001	
Atrial Fibrillation/Flutter-Yes	75/ 321 (23.4%)	70/ 248 (28.2%)	0.83 (0.59, 1.14)	0.25	0.40
Atrial Fibrillation/Flutter-No	384/3768 (10.2%)	536/3842 (14.0%)	0.71 (0.62, 0.81)	<0.0001	
CV Death	174/4089 (4.3%)	213/4090 (5.2%)	0.80 (0.66, 0.98)	0.03	
Atrial Fibrillation/Flutter-Yes	22/ 321 (6.9%)	27/ 248 (10.9%)	0.64 (0.36, 1.12)	0.12	0.35
Atrial Fibrillation/Flutter-No	152/3768 (4.0%)	186/3842 (4.8%)	0.82 (0.66, 1.02)	0.07	
Nonfatal MI	237/4089 (5.8%)	332/4090 (8.1%)	0.70 (0.59, 0.82)	<0.0001	
Atrial Fibrillation/Flutter-Yes	46/ 321 (14.3%)	40/ 248 (16.1%)	0.88 (0.57, 1.34)	0.54	0.17
Atrial Fibrillation/Flutter-No	191/3768 (5.1%)	292/3842 (7.6%)	0.65 (0.54, 0.78)	<0.0001	
Nonfatal Stroke	85/4089 (2.1%)	118/4090 (2.9%)	0.71 (0.54, 0.94)	0.01	
Atrial Fibrillation/Flutter-Yes	14/ 321 (4.4%)	12/ 248 (4.8%)	0.89 (0.41, 1.93)	0.76	0.51
Atrial Fibrillation/Flutter-No	71/3768 (1.9%)	106/3842 (2.8%)	0.67 (0.50, 0.91)	0.0097	
Coronary Revascularization	376/4089 (9.2%)	544/4090 (13.3%)	0.66 (0.58, 0.76)	<0.0001	
Atrial Fibrillation/Flutter-Yes	58/ 321 (18.1%)	53/ 248 (21.4%)	0.83 (0.57, 1.20)	0.32	0.14
Atrial Fibrillation/Flutter-No	318/3768 (8.4%)	491/3842 (12.8%)	0.63 (0.55, 0.73)	<0.0001	
Hospitalization for Unstable Angina	108/4089 (2.6%)	157/4090 (3.8%)	0.68 (0.53, 0.87)	0.002	
Atrial Fibrillation/Flutter-Yes	8/ 321 (2.5%)	19/ 248 (7.7%)	0.32 (0.14, 0.74)	0.005	0.08
Atrial Fibrillation/Flutter-No	100/3768 (2.7%)	138/3842 (3.6%)	0.73 (0.56, 0.94)	0.02	
Total Mortality	274/4089 (6.7%)	310/4090 (7.6%)	0.87 (0.74, 1.02)	0.09	
Atrial Fibrillation/Flutter-Yes	34/ 321 (10.6%)	34/ 248 (13.7%)	0.76 (0.47, 1.23)	0.27	0.57
Atrial Fibrillation/Flutter-No	240/3768 (6.4%)	276/3842 (7.2%)	0.88 (0.74, 1.04)	0.13	

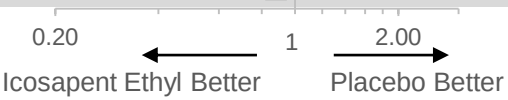


Figure 14.2.105.4.BB

Abbreviations: CI = confidence interval; HR = hazard ratio; Int = interaction; ITT = Intent-to-Treat; pVal = p-value.

Safety Conclusions

- Overall, icosapent ethyl was tolerated as well as placebo
- Total bleeding events were increased with icosapent ethyl and serious bleeding trended toward an increase, but serious bleeding event rates were low
- A higher incidence of atrial fibrillation/flutter was observed with icosapent ethyl
  - Overall rates low; more common as recurrent than new onset
  - Consequences associated with atrial fibrillation/flutter reduced in the full study cohort and in those with atrial fibrillation/flutter
- Safety considerations can be addressed within labeling

Benefit / Risk Considerations

Full ITT Population

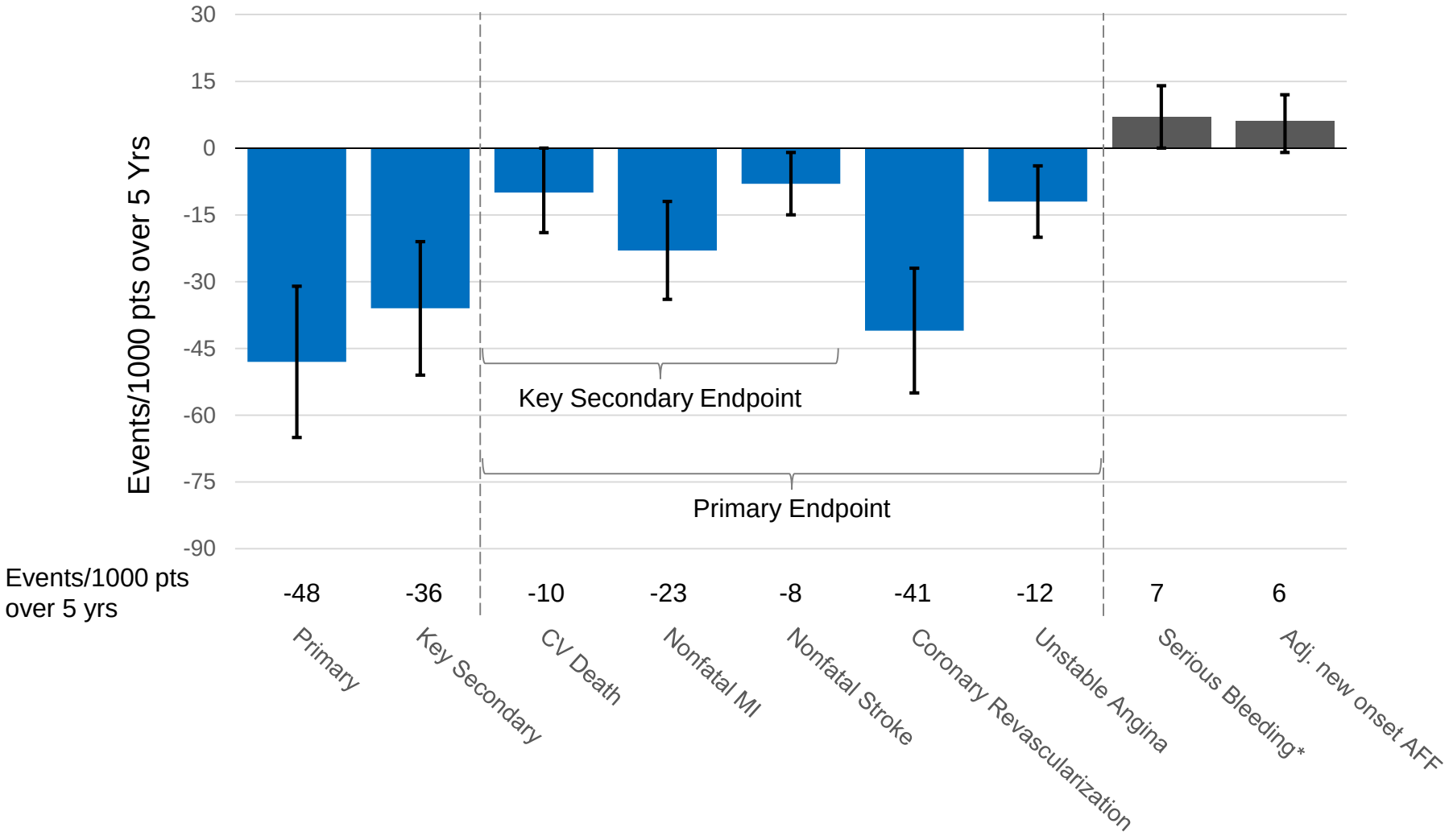


Figure 14.222.1 *Includes hemorrhagic stroke

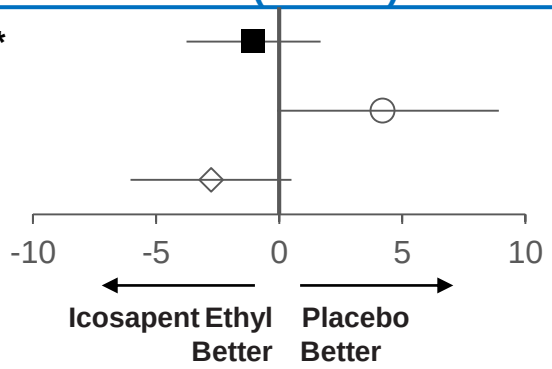
High-risk Primary Prevention with Diabetes

Benefit Across Baseline Risk

High-risk primary prevention patients

- Removing patients with CV history
- Stratified by pooled cohort equation risk score (10-year ASCVD risk score)

	ARD (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	ARD (95% CI)
Primary composite endpoint*		97/ 975 (9.9%)	108/ 983 (11.0%)	-1.04 (-3.77, 1.69)
<10%		16/ 214 (7.5%)	7/ 214 (3.3%)	4.21 (-0.08, 8.92)
≥10%		79/ 754 (10.5%)	101/ 763 (13.2%)	-2.76 (-6.04, 0.50)



*Patients with missing ASCVD risk score are included.

Note: Recategorized CV risk categories excludes patients with MI, Stroke, Coronary Revascularization, Unstable angina, Carotid revascularization and Peripheral Revascularization from Primary Prevention and included in Secondary Prevention

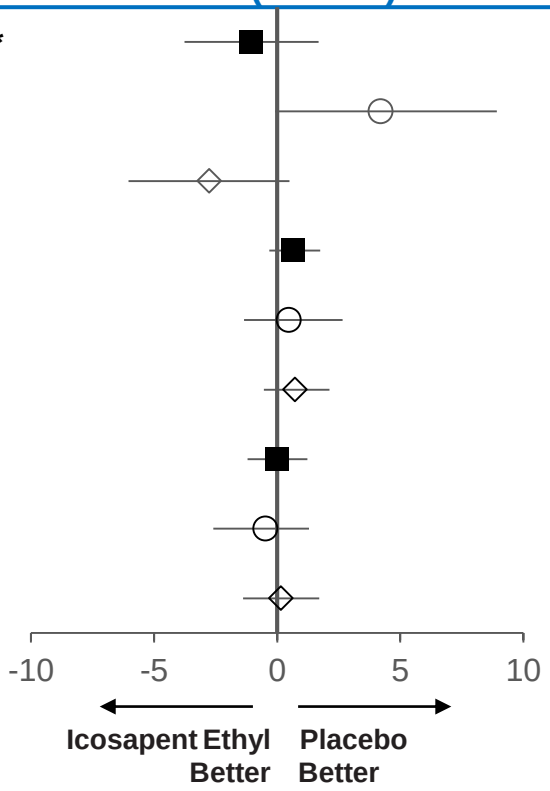
High-risk Primary Prevention with Diabetes

Benefit / Risk Across Baseline Risk

High-risk primary prevention patients

- Removing patients with CV history
- Stratified by pooled cohort equation risk score (10-year ASCVD risk score)

	ARD (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	ARD (95% CI)
Primary composite endpoint*		97/ 975 (9.9%)	108/ 983 (11.0%)	-1.04 (-3.77, 1.69)
<10%		16/ 214 (7.5%)	7/ 214 (3.3%)	4.21 (-0.08, 8.92)
≥10%		79/ 754 (10.5%)	101/ 763 (13.2%)	-2.76 (-6.04, 0.50)
Adj. new onset AFF		13/ 907 (1.4%)	7/ 910 (0.8%)	0.66 (-0.32, 1.75)
<10%		1/ 209 (0.5%)	0/ 207 (0.0%)	0.48 (-1.35, 2.66)
≥10%		12/ 692 (1.7%)	7/ 697 (1.0%)	0.73 (-0.54, 2.12)
Serious bleeding-related disorders*		17/ 975 (1.7%)	17/ 983 (1.7%)	0.01 (-1.20, 1.23)
<10%		0/ 214 (0.0%)	1/ 214 (0.5%)	-0.47 (-2.60, 1.30)
≥10%		17/ 754 (2.3%)	16/ 763 (2.1%)	0.16 (-1.38, 1.71)



*Patients with missing ASCVD risk score are included.

Note: Recategorized CV risk categories excludes patients with MI, Stroke, Coronary Revascularization, Unstable angina, Carotid revascularization and Peripheral Revascularization from Primary Prevention and included in Secondary Prevention

*Includes hemorrhagic stroke

Overall Conclusions

- Compared with placebo, icosapent ethyl 4g/day significantly reduced important CV events by **25%**, including:
  - **31%** reduction in heart attack
  - **28%** reduction in stroke
  - **20%** reduction in death due to cardiovascular causes
  - **30%** reduction in total ischemic events
- Consistent efficacy demonstrated across prespecified testing hierarchy as well as other cardiovascular endpoints and generally across multiple subgroups
- Low rate of adverse effects that can be addressed within labeling
  - Small but significant increase in atrial fibrillation/flutter
  - Increase in all bleeding; trend towards increase in serious bleeding
- Favorable Benefit-Risk profile; including:
  - Secondary prevention
  - High-risk primary prevention with diabetes with 10-year ASCVD risk ≥10%

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019. Bhatt DL. AHA 2018, Chicago.
Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019;73:2791-2802

Agenda

REDUCE-IT History and Program Introduction	**Rebecca Juliano, PhD** *SVP, Clinical Research and Development* *Amarin*
Medical Need	**Michael Miller, MD** *Professor of Cardiovascular Medicine* *Director, Center for Preventive Cardiology* *University of Maryland School of Medicine*
REDUCE-IT Trial Summary • ***Study Overview*** • ***Study Results***	**Deepak L. Bhatt, MD, MPH** *Executive Director of Interventional Cardiovascular Programs, Brigham and Women's Hospital* *Professor, Harvard Medical School*
Clinical Implications of REDUCE-IT	**Ann Marie Navar, MD, PhD** *Assistant Professor of Cardiology* *Duke University School of Medicine* *Duke Clinical Research Institute*
Closing Remarks	**Rebecca Juliano, PhD** *SVP, Clinical Research and Development* *Amarin*

Clinical Implications of REDUCE-IT

Ann Marie Navar, MD, PhD

Assistant Professor of Cardiology

Duke University School of Medicine

Duke Clinical Research Institute

Disclosure

Research support to Duke University for research studies of triglyceride epidemiology, personal consulting fees including advisory board participation.

Clinical Perspective: Unmet Medical Need

- CV disease is a large and growing unmet need in the US[1]
  - One heart attack and one stroke every 40 seconds
  - #1 cause of death in the US
  - $555 billion annual treatment cost and rising
- Elevated TG = marker for particularly at-risk group
  - Increasing prevalence of obesity and diabetes driving increase in prevalence of elevated TG
- Despite effective therapies, high risk of recurrent CV events in those with CVD and high rates of CV events in high-risk diabetes
  - 5.7% annual MACE rate in REDUCE-IT population
- No FDA-approved therapy for CV risk reduction in this population: high-risk including persistently elevated TG

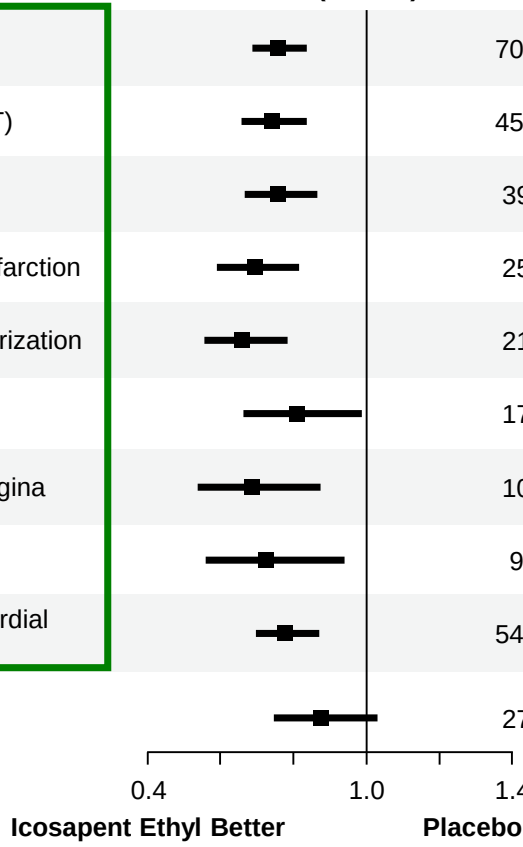
1. AHA: Heart Disease and Stroke Statistics 2018 At-a-Glance

Why Will REDUCE-IT Change My Practice?

- Large, long-term, global, randomized, placebo-controlled outcomes trial
  - Over 8000 patients, 11 countries, 4.9-year median follow-up
- Convincing efficacy
  - Small changes in lipids and CRP in placebo group are insufficient to explain magnitude of benefit
  - RRR in REDUCE-IT consistent with JELIS CVOT
- Magnitude of benefit demonstrated even in otherwise well-managed patients
- Substantial, consistent, and clinically meaningful results across CV endpoints and subgroups

Consistent Efficacy Across CV Events

Endpoint	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	RRR	P-value
Primary Composite (ITT)	705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68–0.83)	25%	<0.001
Key Secondary Composite (ITT)	459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65–0.83)	26%	<0.001
Cardiovascular Death or Nonfatal Myocardial Infarction	392/4089 (9.6%)	507/4090 (12.4%)	0.75 (0.66–0.86)	25%	<0.001
Fatal or Nonfatal Myocardial Infarction	250/4089 (6.1%)	355/4090 (8.7%)	0.69 (0.58–0.81)	31%	<0.001
Urgent or Emergent Revascularization	216/4089 (5.3%)	321/4090 (7.8%)	0.65 (0.55–0.78)	35%	<0.001
Cardiovascular Death	174/4089 (4.3%)	213/4090 (5.2%)	0.80 (0.66–0.98)	20%	0.03
Hospitalization for Unstable Angina	108/4089 (2.6%)	157/4090 (3.8%)	0.68 (0.53–0.87)	32%	0.002
Fatal or Nonfatal Stroke	98/4089 (2.4%)	134/4090 (3.3%)	0.72 (0.55–0.93)	28%	0.01
Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke	549/4089 (13.4%)	690/4090 (16.9%)	0.77 (0.69–0.86)	23%	<0.001
Total Mortality	274/4089 (6.7%)	310/4090 (7.6%)	0.87 (0.74–1.02)	13%	0.09



RRR denotes relative risk reduction

Primary endpoint NNT = 21; key secondary endpoint NNT = 28

Managing Risks in Clinical Practice

- Generally, icosapent ethyl was well-tolerated
- Safety signals do not offset clinical benefit, can be addressed in clinical practice

Managing Risks in Clinical Practice

- Generally, icosapent ethyl was well-tolerated
- Safety signals do not offset clinical benefit, can be addressed in clinical practice
  - Bleeding
    - Absolute rates low
    - Most occurred in patients on antithrombotic therapies; already monitored
    - No difference in fatal bleeds
    - Similar to other clinical trials in ASCVD prevention

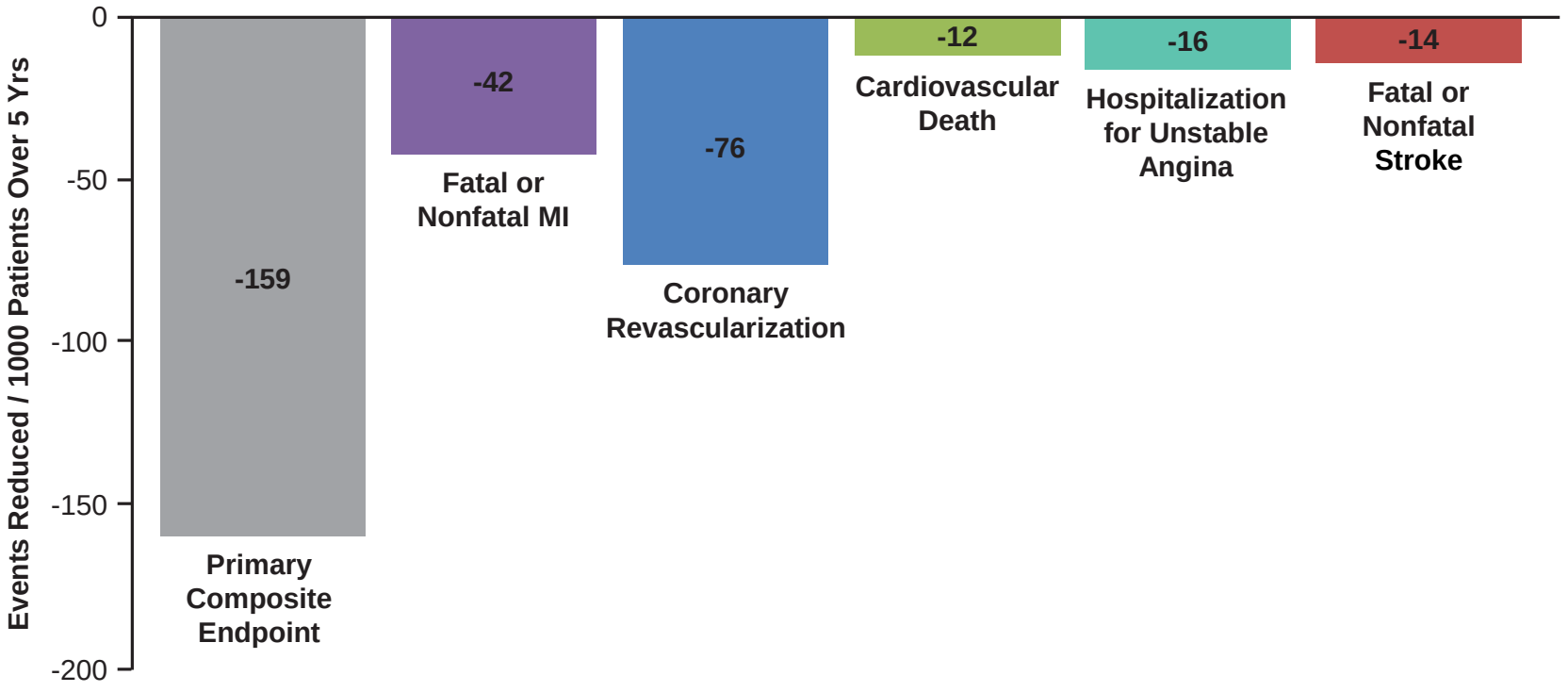
Managing Risks in Clinical Practice

- Generally, icosapent ethyl was well-tolerated
- Safety signals do not offset clinical benefit, can be addressed in clinical practice
  - Atrial fibrillation/flutter
    - Common in clinical practice - primary care and specialists familiar with detection and management
    - Atrial fibrillation was a pre-specified component of a tertiary endpoint (cardiac arrhythmias). Patients were not systematically/continuously monitored for afib
      - Absolute increase in adjudicated new-onset afib 0.6%
      - Difference in reported incident cases could be due to higher incidence vs. increased detection of otherwise asymptomatic cases
    - Most afib risk increase in patients with prior history of atrial fibrillation/flutter
      - Already on treatment, may require adjustment in current rate/rhythm control
      - Should not impact stroke risk (driven by anticoagulation use, not symptoms)
    - Baseline or on-study atrial fibrillation/flutter did not impact effectiveness

Composite MACE, CV death, and stroke (most feared consequence of afib) all reduced

Clinically Meaningful Avoidable Events

Events Avoided per 1000 Patients Treated with Icosapent Ethyl for 5 Years



On average, 1 event reduced per 6 patients treated for 5 years

Adapted from Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019;73:2791-2802.

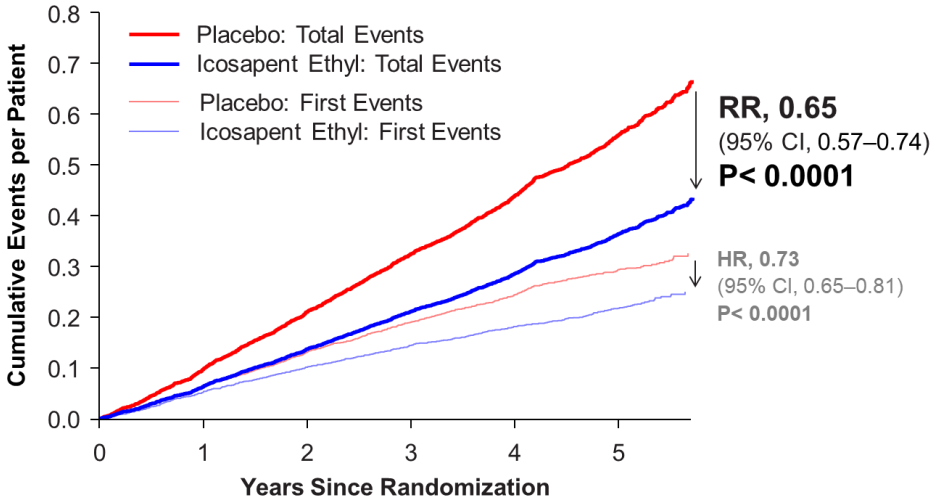
Secondary and Primary Prevention Results

High-risk Primary Prevention Patients Need More Time

First and Total Events by Study Cohort

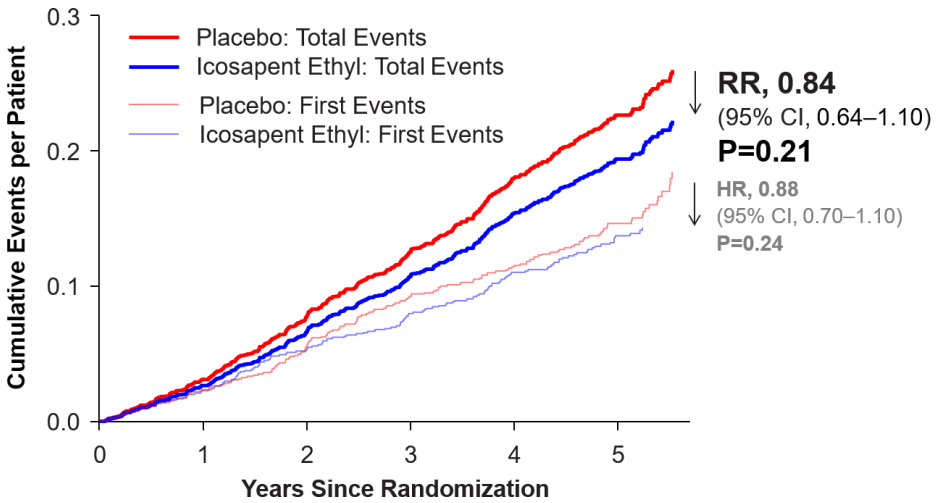
Secondary Prevention

35% RRR



High-risk Primary Prevention with Diabetes

16% RRR



CV Risk Varies Across Patients with Diabetes

- Absolute benefit (NNT) driven by absolute risk of events
- Not all patients with diabetes are the same
- REDUCE-IT population defined high-risk primary prevention patients with diabetes
  - All with persistently elevated TG despite statin therapy, diabetes requiring medication, and at least one additional risk factor
    - Approximately 89% of REDUCE-IT patients had two or more risk factors; the inclusion criteria define a high-risk population

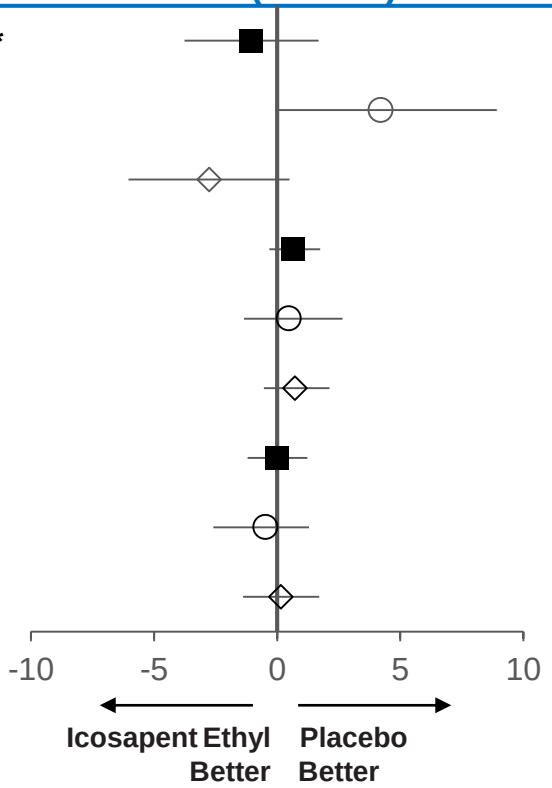
High-risk Primary Prevention with Diabetes

Benefit / Risk Across Baseline Risk

High-risk primary prevention patients

- Removing patients with CV history
- Stratified by pooled cohort equation risk score (10-year ASCVD risk score)

	ARD (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	ARD (95% CI)
Primary composite endpoint*		97/ 975 (9.9%)	108/ 983 (11.0%)	-1.04 (-3.77, 1.69)
<10%		16/ 214 (7.5%)	7/ 214 (3.3%)	4.21 (-0.08, 8.92)
≥10%		79/ 754 (10.5%)	101/ 763 (13.2%)	-2.76 (-6.04, 0.50)
Adj. new onset AFF		13/ 907 (1.4%)	7/ 910 (0.8%)	0.66 (-0.32, 1.75)
<10%		1/ 209 (0.5%)	0/ 207 (0.0%)	0.48 (-1.35, 2.66)
≥10%		12/ 692 (1.7%)	7/ 697 (1.0%)	0.73 (-0.54, 2.12)
Serious bleeding-related disorders*		17/ 975 (1.7%)	17/ 983 (1.7%)	0.01 (-1.20, 1.23)
<10%		0/ 214 (0.0%)	1/ 214 (0.5%)	-0.47 (-2.60, 1.30)
≥10%		17/ 754 (2.3%)	16/ 763 (2.1%)	0.16 (-1.38, 1.71)



*Patients with missing ASCVD risk score are included.

Note: Recategorized CV risk categories excludes patients with MI, Stroke, Coronary Revascularization, Unstable angina, Carotid revascularization and Peripheral Revascularization from Primary Prevention and included in Secondary Prevention

NNT of 96 drops to 36 when considering only patients with ≥10% 10-year risk ASCVD risk

*Includes hemorrhagic stroke

Risk Assessment Already Part of Diabetes Care

- Clinicians are familiar with using risk-based guidelines for primary prevention
- ACC/AHA Guidelines
  - Cholesterol Guidelines use 10-year ASCVD risk to determine statin eligibility and intensity
  - Hypertension Guidelines use 10-year ASCVD risk to determine BP goal

Medical Societies Recognizing Clinical Impact of REDUCE-IT Results

- **ADA Standards of Care**[1]: (Persons with diabetes) ASCVD or other cardiac risk factors on statin with controlled LDL-C, elevated triglycerides (135-499 mg/dL)
- **AHA Science Advisory**[2]: for "improving cardiovascular disease risk in patients with hypertriglyceridemia"
- **ESC/EAS Guidelines**[3]**:** "high-risk" patients with TGs 135-499 mg/dL despite statin treatment
    - High risk=prior ASCVD, diabetes with target organ damage, diabetes with prolonged duration, CKD, high 10-year risk, FH, CKD
- **NLA Scientific Statement**[4]: ASCVD ≥45 years or Type 2 diabetes ≥50 years requiring medication + 1 risk factor + TGs 135-499 mg/dL on high intensity or max tolerated statin
- Therapy cost-effective (ICER)[5]

1. American Diabetes Association. Diabetes Care 2019;42(Suppl. 1):S103–S123. Retrieved from https://hyp.is/JHhz_lCrEembFJ9LIVBZIw; 2. Skulas-Ray AC, Wilson PWF, Harris WS, et al; Circulation. 2019;140:e•••–e•••. doi: 10.1161/CIR.0000000000000709; 3. Mach F, et al. 2019 European Heart Journal (2019) 00, 1-78. doi:10.1093/eurheartj/ehz455; 4.Orringer CE et. al. Journal of Clinical Lipidology (2019), doi: https://doi.org/10.1016/j.jacl.2019.10.014; [5] https://icer-review.org/wp-content/uploads/2019/02/ICER_CVD_Evidence_Report_09122019.pdf

Benefit Risk Ratio is Strongly Favorable

- Unmet need: No FDA-approved therapy for CV risk in high-risk patients with persistent TG elevation despite statin therapy
- Icosapent ethyl was well-tolerated with safety characteristics that can be addressed within clinical practice
- Robust results across CV endpoints
- Icosapent ethyl will be an important addition to armamentarium of treatments for CV risk reduction
- Patients at risk now: prompt approval will prevent missed opportunity for high-risk eligible patients

Agenda

REDUCE-IT History and Program Introduction	**Rebecca Juliano, PhD** *SVP, Clinical Research and Development* *Amarin*
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Closing Remarks	**Rebecca Juliano, PhD** *SVP, Clinical Research and Development* *Amarin*

REDUCE-IT
Closing Remarks

Rebecca Juliano, PhD

SVP, Clinical Research and Development

Amarin

REDUCE-IT
Summary

- Prospective, randomized, double-blind, placebo-controlled, multinational
  - Completed per study design under Special Protocol Assessment agreement
  - 8179 patients from 11 countries treated for a median of 4.9 years
  - Patients were well-managed with modern treatment modalities
  - Quality trial conduct; limited primary analysis missing, 99.8% vital status
- Consistent, statistically and clinically persuasive efficacy
  - Primary MACE endpoint reduced 25% (p=0.00000001)
  - Key secondary hard MACE endpoint reduced 26% (p=0.0000006)
  - Reductions across prespecified hierarchy of endpoints
  - Reductions in each component of the primary and key secondary endpoints
  - Generally consistent findings across patient subgroups
  - Consistent findings across CV-related tertiary and exploratory endpoints
- Well-tolerated with limited safety signals
  - Overall AE and SAE rates were comparable to placebo
  - Bleeding and atrial fibrillation/flutter findings can be addressed in labeling

Bhatt DL, Steg PG, Miller M, et al. N Engl J Med. 2018;380(1):11-22. doi:10.1056/NEJMoa1812792

Amarin Perspective on FDA Items for Consideration

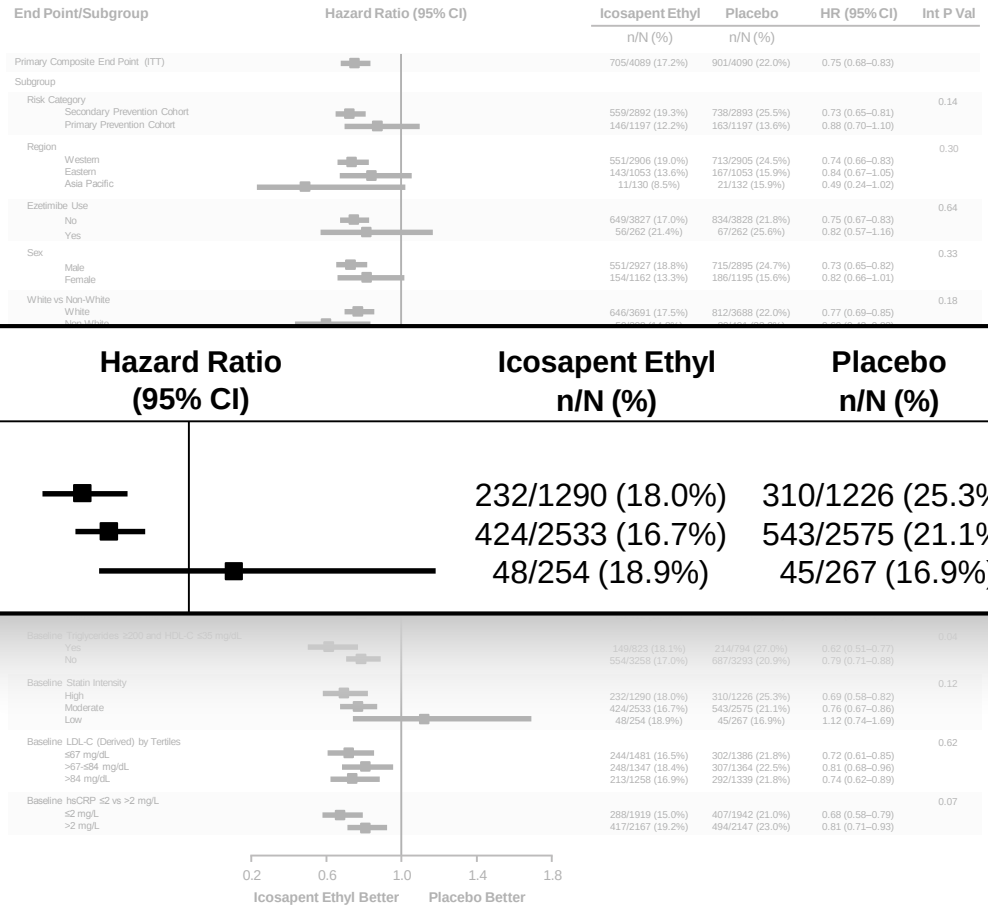
- REDUCE-IT demonstrated CV risk reduction
  - Reductions in the primary and key secondary efficacy endpoints
  - Mineral oil analyses do not alter study overall study conclusions
  - Consistency across CV endpoints and generally across subgroups
  - Each primary composite endpoint component contributed to overall benefit
- Bleeding and atrial fibrillation/flutter can be addressed in labeling
- Favorable benefit / risk remains compelling across subgroups; including:
  - In secondary prevention
  - High-risk primary prevention with diabetes with 10-year ASCVD risk ≥10%
- REDUCE-IT provides sufficient efficacy and safety data to support a CV risk reduction indication for icosapent ethyl
- Amarin looks forward to labeling discussions with FDA toward the goal of final language that reflects REDUCE-IT results

Closing Remarks

- Unmet need for an option to address CV risk beyond current therapies
  - Almost one quarter of REDUCE-IT placebo patients experienced a primary endpoint event
- REDUCE-IT demonstrates a favorable benefit risk profile for the studied high-risk patients
- We thank patients and clinical sites for their dedication and involvement across the multi-year REDUCE-IT study
- With an expanded indication, we look forward to supporting healthcare decision-makers in translating this research into an accessible cost-effective therapy for appropriate patients in need

Backup Slides

BB Figure 9. Primary Endpoint in Subgroups (ITT)
Baseline Statin Intensity



Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Baseline Statin Intensity					0.12
High		232/1290 (18.0%)	310/1226 (25.3%)	0.69 (0.58–0.82)	
Moderate		424/2533 (16.7%)	543/2575 (21.1%)	0.76 (0.67–0.86)	
Low		48/254 (18.9%)	45/267 (16.9%)	1.12 (0.74–1.69)	

BB Table 3. Baseline Characteristics (ITT) [Slide 2 of 4]

Sex, Race, Ethnicity

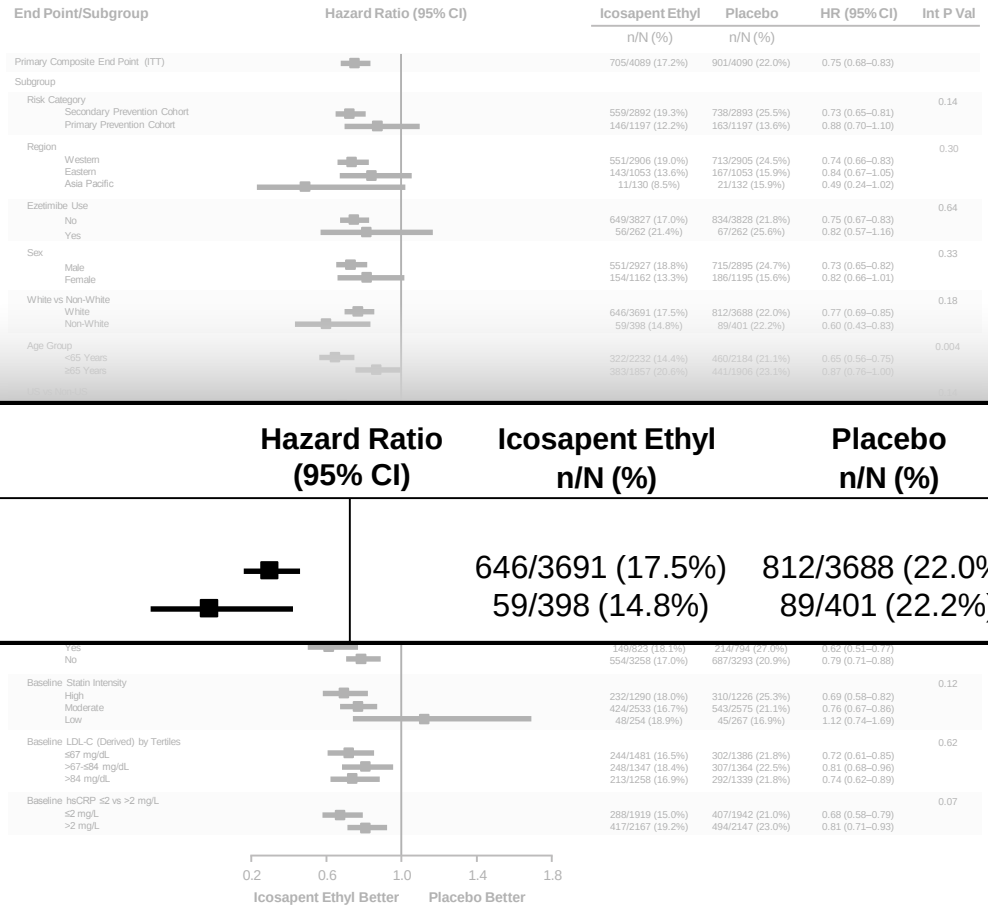
Parameter Statistic	Icosapent ethyl (N=4089)	Placebo (N=4090)	Overall (N=8179)	P-value[1]
Sex, n (%)				0.4245
Male	2927 (71.6)	2895 (70.8)	5822 (71.2)	
Female	1162 (28.4)	1195 (29.2)	2357 (28.8)	
Race, n (%)				0.3415
White	3691 (90.3)	3688 (90.2)	7379 (90.2)	
Black or African American	69 (1.7)	89 (2.2)	158 (1.9)	
Asian	225 (5.5)	221 (5.4)	446 (5.5)	
American Indian or Alaska Native	18 (0.4)	11 (0.3)	29 (0.4)	
Native Hawaiian or Other Pacific Islander	7 (0.2)	3 (0.1)	10 (0.1)	
Multiple	49 (1.2)	42 (1.0)	91 (1.1)	
Other	30 (0.7)	35 (0.9)	65 (0.8)	
Missing	0 (0.0)	1 (0.0)	1 (0.0)	
Ethnicity, n (%)				0.0877
Hispanic or Latino	188 (4.6)	157 (3.8)	345 (4.2)	
Not Hispanic or Latino	3901 (95.4)	3933 (96.2)	7834 (95.8)	

Abbreviations: BMI = body mass index; CRF = case report form; eGFR = estimated glomerular filtration rate; ITT = Intention-to-Treat; Max = maximum; Min = minimum; SD = standard deviation.

Note: Percentages were based on the number of patients randomized to each treatment group in the ITT population (N) except as noted below.

1 To assess balance between treatment groups, p-values were reported from a chi-square test for categorical variables and a t test for continuous variables. Missing categories were excluded from any comparisons.

BB Figure 9. Primary Endpoint in Subgroups (ITT)
White vs Non-White



Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
White vs Non-White					0.18
White		646/3691 (17.5%)	812/3688 (22.0%)	0.77 (0.69–0.85)	
Non-White		59/398 (14.8%)	89/401 (22.2%)	0.60 (0.43–0.83)	

Group Sequential P-Value Boundaries According to Two Actual Interim Analyses Information Fractions

Look	Analysis	No. of Events	Information Fraction	Efficacy Boundary (1-sided alpha level)	Efficacy Boundary (2-sided alpha level)
1	IA #1	953	59.3%	0.00356	0.0071
2	IA #2	1218	75.8%	0.00885	0.0177
3	Final	1606	100%	0.02186	0.0437

IA = Interim analysis; No. = Number.

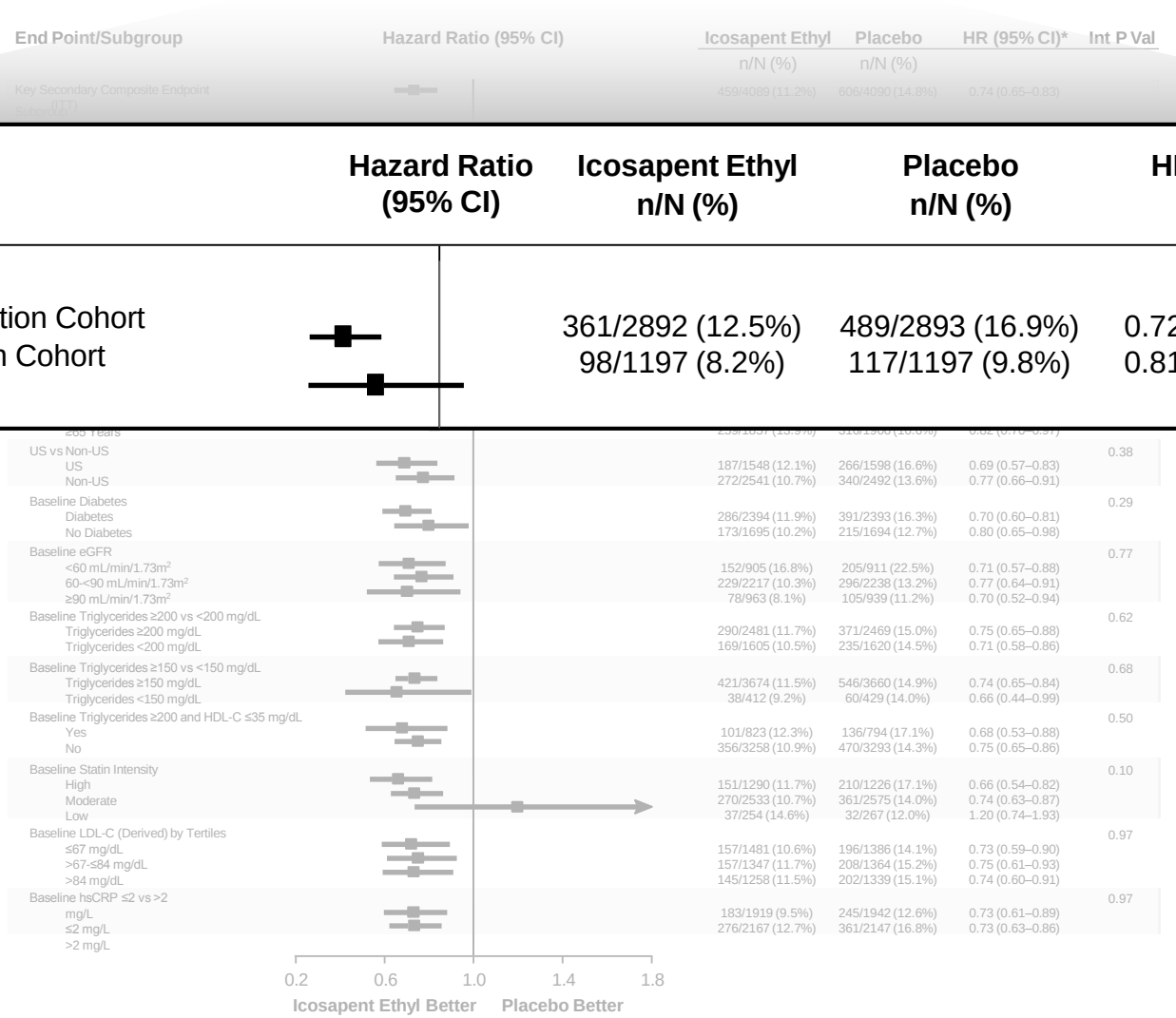
BB Table 27. Primary Endpoint Adjusted for Post-Baseline Lipids/Biomarkers as Time Varying Covariates (ITT)

	Treatment (Icosapent Ethyl vs Placebo)		Lipid Biomarker Covariate		
				Slope Value in Hazard Ratio	
Lipid Covariate [1]	HR (95% CI) for Treatment (Adjusting Covariate[2])	Significance P-value[3]	HR (95% CI) for One Unit Covariate Change[4]	Estimated Slope[5]	Standard Error[5]
Triglycerides (mg/dL)	0.772 (0.700, 0.853)	<0.0001	1.001 (1.000, 1.001)	0.000700	0.000113
LDL-C derived (mg/dL)	0.752 (0.681, 0.830)	0.8043	1.000 (0.998, 1.002)	-0.000252	0.001015
LDL-C (Ultracentrifugation) (mg/dL)	0.759 (0.687, 0.839)	0.9766	1.000 (0.998, 1.002)	0.000029	0.000982
LDL-C (Friedewald) (mg/dL)	0.760 (0.688, 0.839)	0.0517	1.002 (1.000, 1.003)	0.001617	0.000831
LDL-C (Hopkins) (mg/dL)	0.772 (0.699, 0.852)	<0.0001	1.004 (1.002, 1.006)	0.003996	0.000810
HDL Cholesterol-CDC (mg/dL)	0.730 (0.661, 0.806)	<0.0001	0.978 (0.973, 0.983)	-0.022291	0.002518
Non-HDL Cholesterol (mg/dL)	0.784 (0.710, 0.866)	<0.0001	1.004 (1.003, 1.005)	0.003865	0.000592
Apolipoprotein B (mg/dL)	0.762 (0.689, 0.841)	0.0312	1.002 (1.000, 1.005)	0.002452	0.001138
hsCRP (mg/L)	0.758 (0.686, 0.836)	0.0043	1.007 (1.002, 1.011)	0.006584	0.002304
RLP-C (mg/dL)	0.784 (0.709, 0.866)	<0.0001	1.008 (1.006, 1.011)	0.008162	0.001213

[1] Time varying biomarker is derived as the last non-missing biomarker data collected prior to the onset of the efficacy endpoint.
[2] Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment and time varying biomarker as the covariates, and stratified by geographic region, CV risk category, and use of ezetimibe.
[3] P-value for testing significance of covariate in the Cox proportional hazard model.
[4] Hazard ratio for one unit increase of covariate from the Cox proportional hazard model.
[5] Estimated slope and its standard error for covariate from the Cox proportional hazard model.

BB Figure 10. Key Secondary Endpoint in Subgroups (ITT)
CV Risk Category

Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Risk Category					0.41
Secondary Prevention Cohort		361/2892 (12.5%)	489/2893 (16.9%)	0.72 (0.63–0.82)	
Primary Prevention Cohort		98/1197 (8.2%)	117/1197 (9.8%)	0.81 (0.62–1.06)	

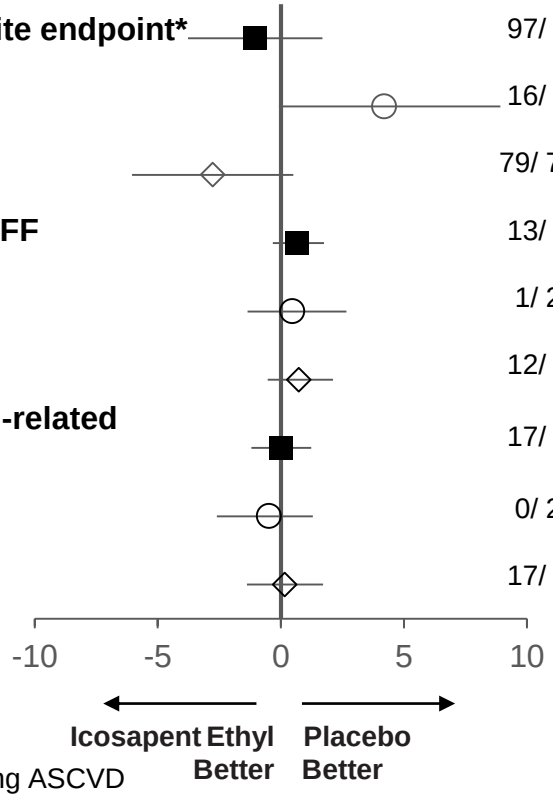


High-risk Primary Prevention with Diabetes

Benefit / Risk Across Baseline Risk Score

High-risk primary prevention patients

- Removing patients with CV history
- Stratified by pooled cohort equation risk score (10-year ASCVD risk score)



	ARD (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	ARD (95% CI)	Icosapent Ethyl vs. Placebo HR (95% CI)
Primary composite endpoint*		97/ 975 (9.9%)	108/ 983 (11.0%)	-1.04 (-3.77, 1.69)	0.88 (0.70, 1.10)
<10%		16/ 214 (7.5%)	7/ 214 (3.3%)	4.21 (-0.08, 8.92)	2.29 (0.94, 5.58)
≥10%		79/ 754 (10.5%)	101/ 763 (13.2%)	-2.76 (-6.04, 0.50)	0.77 (0.57, 1.04)
Adj. new onset AFF		13/ 907 (1.4%)	7/ 910 (0.8%)	0.66 (-0.32, 1.75)	
<10%		1/ 209 (0.5%)	0/ 207 (0.0%)	0.48 (-1.35, 2.66)	
≥10%		12/ 692 (1.7%)	7/ 697 (1.0%)	0.73 (-0.54, 2.12)	
Serious bleeding-related disorders*		17/ 975 (1.7%)	17/ 983 (1.7%)	0.01 (-1.20, 1.23)	
<10%		0/ 214 (0.0%)	1/ 214 (0.5%)	-0.47 (-2.60, 1.30)	
≥10%		17/ 754 (2.3%)	16/ 763 (2.1%)	0.16 (-1.38, 1.71)	

Note: Recategorized CV risk categories excludes patients with MI, Stroke, Coronary Revascularization, Unstable angina, Carotid revascularization and Peripheral Revascularization from Primary Prevention and included in Secondary Prevention

*Patients with missing ASCVD risk score are included.

*Includes hemorrhagic stroke